

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 207/333, A61K 31/40, C07D 401/04, 207/33, 207/337, 207/36, 207/34	A1	(11) International Publication Number: WO 98/25896 (43) International Publication Date: 18 June 1998 (18.06.98)
--	-----------	---

(21) International Application Number: PCT/US97/22488

(22) International Filing Date: 9 December 1997 (09.12.97)

(30) Priority Data:
60/032,688 10 December 1996 (10.12.96) US(71) Applicant (for all designated States except US): G.D. SEARLE
& CO. [US/US]; Corporate Patent Dept., P.O. Box 5110,
Chicago, IL 60680-5110 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): KHANNA, Ish, K.
[IN/US]; 149 Brandywine Court, Vernon Hills, IL 60061
(US). WEIER, Richard, M. [US/US]; 240 Hickory Court,
Lake Bluff, IL 60044 (US). YU, Yi [CN/US]; 9065 Gross
Point Road, Skokie, IL 60077 (US).(74) Agents: BULOCK, Joseph, W. et al.; G.D. Searle & Co.,
Corporate Patent Dept., P.O. Box 5110, Chicago, IL
60680-5110 (US).(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR,
BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE,
GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM,
KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
ML, MR, NE, SN, TD, TG).

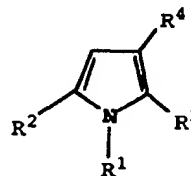
Published

With international search report.

(54) Title: SUBSTITUTED PYRROLYL COMPOUNDS FOR THE TREATMENT OF INFLAMMATION

(57) Abstract

A class of pyrrolyl derivatives is described for use in treating inflammation and inflammation-related disorders. Compounds of particular interest are defined by formula (I), wherein at least one of R¹ and R² is phenyl substituted with methylsulfonyl or aminosulfonyl.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**SUBSTITUTED PYRROLYL COMPOUNDS
FOR THE TREATMENT OF INFLAMMATION**

FIELD OF THE INVENTION

5

This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to compounds, compositions and methods for treating cyclooxygenase-2 mediated disorders, such as inflammation and arthritis.

10

BACKGROUND OF THE INVENTION

Prostaglandins play a major role in the inflammation process and the inhibition of prostaglandin production, especially production of PGG₂, PGH₂ and PGE₂, has been a common target of antiinflammatory drug discovery. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatening ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

25
30

Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation (named "cyclooxygenase-2 (COX-2)" or "prostaglandin-G/H synthase II") provides a viable target of

35

inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

The references below that disclose
5 antiinflammatory activity, show continuing efforts to find a safe and effective antiinflammatory agent. The novel pyrroles disclosed herein are such safe and also effective antiinflammatory agents furthering such efforts. The substituted pyrrolyl compounds
10 disclosed herein preferably selectively inhibit cyclooxygenase-2 over cyclooxygenase-1.

Pyrroles have been described for various uses, including the treatment of inflammation.

US Patent No. 5,219,856, to R. Olson,
15 generically describes pyrrole-containing angiotensin-II inhibitors. US Patent No. 5,236,943, to Heitsch et al., generically describes pyrrole containing angiotensin-II inhibitors.

US Patent No. 5,128,485, to V. Kameswaran,
20 describes a process for preparing 2-phenyl-5-trifluoromethylpyrroles. EP 492093, published July 1, 1992, describes a similar process.

U.S. Patent No. 5,032,590, to Hubsch et al., describes 1,2-diphenyl-3-(4-fluorophenyl)-5-
25 isopropylpyrrole as an intermediate in the preparation of a hydroxylamine substituted pyrrole.

H. Stetter and M. Schreckenber (Chem. Ber.,
107, 2453 (1974)) describe the synthetic preparation of 1,2-diaryl pyrroles, and specifically, 2-(4-
30 chlorophenyl)-5-methyl-1-phenylpyrrole. F. Cerreto, et al. [Eur. J. Med. Chem, 27, 701 (1992)] describe the 1,5-diaryl-2-methylpyrroles as having anti-Candida activity. M. Scalzo et al. [Il Farmaco Ed. Sc., 43, 665 (1988)] describe 1,5-substituted
35 pyrroles as having antibacterial activity. M. Scalzo et al. [Il Farmaco Ed. Sc., 43, 677 (1988)] describe other 1,5-substituted pyrroles as having antibacterial activity. M. Scalzo et al. [Eur. J.

Med. Chem, 23, 587 (1988)] describe 2-methyl-5-(4-nitrophenyl)-1-phenylpyrroles as having antibacterial activity.

- C. Gillet, et al [*Eur. J. Med. Chem*, 11, 173 (1976)] describe the 1,5-diaryl-3-pyrrole acetic acids as having antiinflammatory activity. German Patent DE 2,261,965 describes 2-methyl-1-phenylpyrroles as having antiinflammatory activity. Belgian Patent 633,582 describes 1-aryl-5-(4-alkoxyphenyl)-2-pyrrole propanoic acids as anticholesterolaemic agents. G. Thiault et al. [*Il Farmaco Ed. Sc.*, 39, 524 (1984)] describe 1,5-substituted pyrroles as having analgesic and antiinflammatory activity. G. Thiault et al. [*Il Farmaco Ed. Sc.*, 39, 765 (1984)] describe other 1,5-substituted pyrroles as having analgesic and antiinflammatory activity. U.S. Patent No. 4,694,018, issued to L. Chin, describes 1-(halophenyl)-5-phenyl-2-pyrrole propanoic acid derivatives as 5-lipoxygenase inhibitors. U.S. Patent No. 5,096,919, issued to Wasley et al., describes 1-pyrrole phenyl hydroxamic acid derivatives as 5-lipoxygenase inhibitors.

- U.S. Patent No. 4,267,184, issued to S. Cherkofsky, describes 4,5-aryl-2-thiopyrroles as antiinflammatory agents. U.S. Patent No. 4,267,190, issued to S. Cherkofsky, describes 4,5-aryl-2-methanethiolpyrroles as antiinflammatory agents. U.S. Patent No. 4,335,136, issued to S. Cherkofsky, describes 4,5-aryl-2-methanaminepyrroles as antiinflammatory agents. U.S. Patent No. 4,267,184, issued to S. Cherkofsky, describes 4,5-aryl-2-halopyrroles as antiinflammatory agents. U.S. Patent No. 3,531,497, issued to G. Youngdale, describes 2,4,5-triphenylpyrroles as antiinflammatory agents. U.S. Patent No. 4,267,184, issued to S. Cherkofsky, describes 4,5-phenylpyrroles as antiinflammatory agents. U.S.

Patent No. 5,474,995, issued to Ducharme et al., describes 4,5-phenylpyrroles as cyclooxygenase-2 inhibitors. W. Wilkerson et al. [*Med. Chem. Res.*, **5**, 399 (1995)] describe 4,5-diarylpyrroles as COX-2 inhibitors. W. Wilkerson et al. [*J. Med. Chem.*, **38**, 3895 (1995)] describe 4,5-diarylpyrroles as COX-2 inhibitors. PCT patent document WO94/15932, published July 21, 1994, describes 3,4-diphenylpyrroles as inhibiting cyclooxygenase-2.

10 US Patent No. 5,187,185, to Outcalt, et al., describes substituted 1-arylpyrroles as pesticides. European patent document EP 372,982, published June 13, 1990, describes similar compounds.

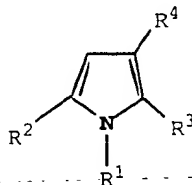
US Patent No. 3,427,305, to L. Chinn, describes 15 1-[4-(aminosulfonyl)phenyl]pyrrole propanoic acids as being antiinflammatory. Specifically, 1-(4-(aminosulfonyl)phenyl)-5-(4-fluorophenyl)-2-pyrrole propanoic acid is described.

British patent GB 1,263,940 describes 1- 20 phenylpyrroles as having antiinflammatory activity. Specifically, 4-[2-methyl-5-phenylpyrrol-1-yl]benzenesulfonamide is described.

The invention's pyrrolyl compounds are found to show usefulness as antiinflammatory agents with 25 minimal side effects.

DESCRIPTION OF THE INVENTION

A class of substituted pyrrolyl compounds 30 useful in treating inflammation-related disorders is defined by Formula I:



I

- wherein R^1 and R^2 are independently selected from aryl, cycloalkyl, cycloalkenyl and heterocyclyl, wherein R^1 and R^2 are optionally substituted at a substitutable position with one or more radicals
- 5 independently selected from alkylsulfonyl, aminosulfonyl, haloalkylsulfonyl, halo, alkylthio, alkylsulfinyl, alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, haloalkoxy, amino,
- 10 alkylamino, arylamino and nitro;
- wherein R^3 is a radical selected from hydrido, halo, methyl and alkoxycarbonylalkyl; and
- wherein R^4 is a radical selected from hydrido, halo, alkyl, haloalkyl, cyano, alkoxycarbonyl,
- 15 carboxyl, formyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkylsulfonyl, haloalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, hydroxyalkyl, mercaptoalkyl, alkoxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, aralkyloxyalkyl,
- 20 heteroarylalkyloxyalkyl, alkylthioalkyl, arylthioalkyl, heteroarylthioalkyl, aralkylthioalkyl, heteroarylalkylthioalkyl, haloalkylcarbonyl, haloalkyl(hydroxy)alkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl,
- 25 heteroarylalkylcarbonyl, carboxyalkyl, alkoxycarbonylalkyl, alkylcarbonyloxyalkyl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, aralkylaminoalkyl, heteroarylaminoalkyl, heteroarylalkylaminoalkyl, alkoxy, and aryloxy;
- 30 provided at least one of R^1 and R^2 is phenyl substituted with methylsulfonyl or aminosulfonyl; and further provided R^3 is hydrido when R^1 is phenyl substituted with aminosulfonyl or methylsulfonyl;
- or a pharmaceutically-acceptable salt thereof.
- 35 Compounds of Formula I would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other cyclooxygenase-2 mediated disorders, such as, as an analgesic in the

treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds of the invention would be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, skin-related conditions such as psoriasis, eczema, burns and dermatitis, and from post-operative inflammation including from ophthalmic surgery such as cataract surgery and refractive surgery. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compounds of the invention would be useful for the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix and skin. Compounds of the invention would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like. The compounds would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis.

The compounds would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, and central nervous system damage resulting from stroke, ischemia and trauma. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and atherosclerosis. The compounds would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB₄ receptor antagonists and LTA₄ hydrolase inhibitors.

Suitable LTA₄ hydrolase inhibitors include RP-64966, (S,S)-3-amino-4-(4-benzyloxyphenyl)-2-hydroxybutyric acid benzyl ester (Scripps Res. Inst.), N-(2(R)-(cyclohexylmethyl)-3-(hydroxycarbamoyl)propionyl)-L-alanine (Searle), 7-(4-(4-ureidobenzyl)phenyl)heptanoic acid (Rhône-Poulenc Rorer), and 3-(3-(1E,3E-tetradecadienyl)-2-oxiranyl)benzoic acid lithium salt (Searle).

Suitable LTB₄ receptor antagonists include, among others, ebselen, linazolast, ontazolast, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C,

Leo Denmark compound ETH-615, Merck compound MAFP, Terumo compound TMK-688, Tanabe compound T-0757, Lilly compounds LY-213024, LY-210073, LY223982, LY233469, and LY255283, LY-293111, 264086 and
5 292728, ONO compounds ONO-LB457, ONO-4057, and ONO-LB-448, Shionogi compound S-2474, calcitrol, Lilly compounds Searle compounds SC-53228, SC-41930, SC-50605 and SC-51146, Warner Lambert compound BPC 15, SmithKline Beecham compound SB-
10 209247 and SK&F compound SKF-104493. Preferably, the LTB₄ receptor antagonists are selected from calcitrol, ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057,
15 and Terumo compound TMK-688.

Suitable 5-LO inhibitors include, among others, Abbott compounds A-76745, 78773 and ABT761, Bayer Bay-x-1005, Cytomed CMI-392, Eisai E-3040, Scotia Pharmaceutica EF-40, Fujirebio F-
20 1322, Merckle ML-3000, Purdue Frederick PF-5901, 3M Pharmaceuticals R-840, rilopirox, flobufen, linasolast, lonapolene, masoprocol, ontasolast, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem
25 phosphate, and bunaprolast.

The present compounds may also be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists,
30 non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. More
35 preferred would be combinations with compounds selected from morphine, meperidine, codeine, --- pentazocine, buprenorphine, butorphanol, dezocine, meptazinol, hydrocodone, oxycodone, methadone,

- Tramadol [(+) enantiomer], DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI-204448, acetaminophen (paracetamol), propoxyphene, nalbuphine, E-4018, filenadol, mirfentanil,
- 5 amitriptyline, DuP631, Tramadol [(-) enantiomer], GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate, Dynorphine A, E-2078, AXC3742, SNX-111, ADL2-1294, ICI-204448, CT-3, CP-99,994, and CP-99,994.
- 10 The present invention preferably includes compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} equal to or less than about 0.2 μM , and also have a selectivity ratio of
- 15 cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1.0 μM , and more preferably of greater than 10 μM . Such
- 20 preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

A preferred class of compounds consists of those compounds of Formula I wherein R^1 and R^2 are

25 independently selected from phenyl, lower cycloalkyl, lower cycloalkenyl and 5- or 6-membered heteroaryl, wherein R^1 and R^2 are optionally substituted at a substitutable position with one or more radicals independently selected from lower

30 alkylsulfonyl, aminosulfonyl, lower haloalkylsulfonyl, halo, lower alkylthio, lower alkyl, cyano, carboxyl, lower alkoxycarbonyl, lower alkylcarbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower alkoxyalkyl, lower

35 haloalkoxy, amino, lower alkylamino, arylamino and nitro; wherein R^3 is a radical selected from hydrido, halo, methyl and lower alkoxycarbonylalkyl; and wherein R^4 is a radical selected from hydrido,

halo, lower alkyl, lower haloalkyl, cyano, lower
alkoxycarbonyl, carboxyl, formyl, phenyl, 5- or 6-
membered heteroaryl, lower aralkyl, lower
heteroarylalkyl, lower alkylsulfonyl, lower
5 haloalkylsulfonyl, phenylsulfonyl, 5- or 6-membered
heteroarylsulfonyl, lower hydroxyalkyl, lower
mercaptoalkyl, lower alkoxyalkyl, lower
phenyloxyalkyl, lower heteroaryloxyalkyl, lower
aralkyloxyalkyl, lower heteroarylalkyloxyalkyl,
10 lower alkylthioalkyl, lower phenylthioalkyl, lower
heteroarylthioalkyl, lower aralkylthioalkyl, lower
heteroarylalkylthioalkyl, lower haloalkylcarbonyl,
lower haloalkyl(hydroxy)alkyl, lower alkylcarbonyl,
phenylcarbonyl, lower aralkylcarbonyl, 5- or 6-
15 membered heteroarylcarbonyl, 5- or 6-membered
heteroarylalkylcarbonyl, lower carboxyalkyl, lower
alkoxycarbonylalkyl, lower alkylcarbonyloxyalkyl,
lower aminoalkyl, lower alkylaminoalkyl, lower
phenylaminoalkyl, lower aralkylaminoalkyl, lower
20 heteroarylaminoalkyl, lower
heteroarylalkylaminoalkyl, lower alkoxy, and
phenyloxy; or a pharmaceutically-acceptable salt
thereof.

A class of compounds of particular interest
25 consists of those compounds of Formula I wherein R¹
and R² are independently selected from phenyl,
cyclohexyl, cyclohexenyl, benzofuryl, benzodioxolyl,
furyl, imidazolyl, thienyl, thiazolyl, pyrrolyl,
oxazolyl, isoxazolyl, triazolyl, pyrimidinyl,
30 isoquinolyl, quinolinyl, benzimidazolyl, indolyl,
pyrazolyl and pyridyl, wherein R¹ and R² are
optionally substituted at a substitutable position
with one or more radicals independently selected
from methylsulfonyl, aminosulfonyl,
35 fluoromethylsulfonyl, difluoromethylsulfonyl,
fluoro, chloro, bromo, methylthio, methyl, ethyl,
isopropyl, tert-butyl, isobutyl, pentyl, hexyl,
cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl,

- isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, methylcarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, *n*-butoxy, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, trifluoromethoxy, amino, methylamino, *N,N*-dimethylamino, phenylamino and nitro; wherein R³ is a radical selected from hydrido, fluoro, chloro, bromo, methyl, ethoxycarbonylethyl, and methoxycarbonylmethyl; and wherein R⁴ is a radical selected from hydrido, fluoro, chloro, bromo, methyl, ethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyano, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, carboxyl, formyl, phenyl, benzyl, phenylethyl, phenylpropyl, methylsulfonyl, phenylsulfonyl, trifluoromethylsulfonyl, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, methylcarbonyl, ethylcarbonyl, trifluoromethylcarbonyl, trifluoro(hydroxy)ethyl, phenylcarbonyl, benzylcarbonyl, methoxycarbonylmethyl, ethoxycarbonylethyl, carboxymethyl, carboxypropyl, methylcarbonyloxymethyl, phenyloxy, phenyloxymethyl, thienyl, furyl, and pyridyl, wherein the thienyl, furyl, pyridyl and phenyl radicals are optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl,

trifluoro(hydroxy
wherein R⁵ is meth
wherein R⁶ is one
selected from hydr
ethyl, trifluorome
pharmaceutically-a

Within Formul
compounds of high
III:



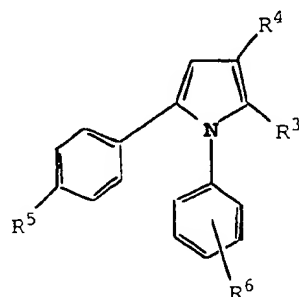
wherein R³ is
selected from hydr
haloalkylsulfonyl,
lower alkylcarbony
phenylcarbonyl, lo
alkylcarbonyloxyal
wherein R⁷ is one
selected from hydr
alkylcarbonyl, and
methylsulfonyl or
acceptable salt th

A class of co
consists of those
R³ is hydrido; whe
hydrido, trifluoro
cyano, trifluorome
methylcarbonyl, ph
trifluoromethylcarl
methylcarbonyloxyme
radicals independe

heptafluoropropyl, difluorochloromethyl,
dichlorofluoromethyl, difluoroethyl, difluoropropyl,
dichloroethyl, dichloropropyl, hydroxyl, methoxy,
methylenedioxy, ethoxy, propoxy, n-butoxy,
5 hydroxymethyl, hydroxyethyl and trifluoromethoxy; or
a pharmaceutically-acceptable salt thereof.

Within Formula I there is a subclass of
compounds of high interest represented by Formula
II:

10



II

wherein R³ is a radical selected from hydrido,
methyl and lower alkoxy carbonylalkyl; wherein R⁴ is
15 radical selected from hydrido, halo, cyano, formyl,
lower haloalkylsulfonyl, lower haloalkyl, lower
hydroxyalkyl, lower alkylcarbonyl, lower aryloxyalk
lower haloalkylcarbonyl, phenylcarbonyl, lower
alkylcarbonyloxyalkyl and lower haloalkylhydroxyalk
20 wherein R⁵ is methylsulfonyl or aminosulfonyl; and
wherein R⁶ is one or more radicals independently
selected from hydrido, halo, lower alkyl, lower
alkylcarbonyl, and lower haloalkyl; or a
pharmaceutically-acceptable salt thereof.

25 A class of compounds of particular interest
consists of those compounds of Formula II wherein R
is a radical selected from hydrido, methyl and
ethoxycarbonyl ethyl; wherein R⁴ is a radical
selected from hydrido, trifluoroethyl, chloro,
30 bromo, formyl, cyano, trifluoromethylsulfonyl,
hydroxymethyl, methylcarbonyl, phenylcarbonyl,
phenyloxymethyl, trifluoromethylcarbonyl,

fluoro, chloro, methyl, ethyl, trifluoromethyl and methylcarbonyl; and wherein R⁸ is methylsulfonyl or aminosulfonyl; or a pharmaceutically-acceptable salt thereof.

- 5 A family of specific compounds of particular interest within Formula I consists of compounds and pharmaceutically-acceptable salts thereof as follows:

- 10 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-phenyl-1H-pyrrole;
1-(3,4-difluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
15 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-[4-(trifluoromethyl)phenyl]-1H-pyrrole;
2-methyl-1-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
20 1-[4-[2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-1-yl]phenyl]ethanone;
1-cyclohexyl-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
2-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
25 4-[2-(4-fluorophenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
30 4-[1-(4-fluorophenyl)-5-methyl-1H-pyrrol-2-yl]benzenesulfonamide;
ethyl 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-2-propanoate;
2,2,2-trifluoro-1-[1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]ethanone;
35 1-[1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]ethanone;

- 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]-phenylmethanone;
- 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-3-[(trifluoromethyl)sulfonyl]-1H-pyrrole;
- 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-3-carbonitrile;
- 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-3-carboxaldehyde;
- 3-bromo-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 3-chloro-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-3-methanol;
- [1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]methyl acetate;
- 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]- α,α,α -(trifluoromethyl)-1H-pyrrole-3-methanol;
- 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-3-(2,2,2-trifluoroethyl)-1H-pyrrole;
- 3-[(3-chlorophenoxy)methyl]-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 3-[(4-chlorophenoxy)methyl]-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 3-fluoro-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(4-pyridyl)-1H-pyrrole;
- 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(3-pyridyl)-1H-pyrrole;
- 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(2-pyridyl)-1H-pyrrole;

- 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(4-methyl-2-pyridyl)-1H-pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(4-methyl-3-pyridyl)-1H-pyrrole;
5 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(5-methyl-2-pyridyl)-1H-pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(5-methyl-3-pyridyl)-1H-pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(3-methyl-2-pyridyl)-1H-pyrrole;
10 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(2-methyl-3-pyridyl)-1H-pyrrole;
1-(4-chlorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
15 2-methyl-1-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
2-methyl-1-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
1-(4-methoxyphenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
20 1-(3-fluoro-4-methoxyphenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
1-(3-chloro-4-methoxyphenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
25 1-(3,5-dichloro-4-methoxyphenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
1-(3,5-difluoro-4-methoxyphenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
1-(3-chloro-4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
30 1-(4-hydroxyphenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
1-(4-hydroxymethylphenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
35 1-[4-[2-methyl-5-[4-(aminosulfonyl)phenyl]-1H-pyrrol-1-yl]phenyl]ethanone;

- 4-[1-(cyclohexyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-phenyl-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(3,4-difluorophenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
5 4-[1-(4-trifluoromethylphenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(4-methylphenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
10 4-[2-methyl-1-(4-pyridyl)-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
4-[2-methyl-1-(4-methylthiophenyl)-1H-pyrrol-5-yl]benzenesulfonamide;
15 4-[2-methyl-1-(4-methylsulfinylphenyl)-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(4-methoxyphenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
20 4-[1-(3-fluoro-4-methoxyphenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(3-chloro-4-methoxyphenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(3,5-dichloro-4-methoxyphenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
25 4-[1-(3,5-difluoro-4-methoxyphenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(3-chloro-4-fluorophenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
30 4-[1-(4-hydroxyphenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(4-hydroxymethylphenyl)-2-methyl-1H-pyrrol-5-yl]benzenesulfonamide;
35 5-[4-(methylsulfonyl)phenyl]-1-(4-pyridyl)-1H-pyrrole;
5-[4-(methylsulfonyl)phenyl]-1-(3-pyridyl)-1H-pyrrole;
5-[4-(methylsulfonyl)phenyl]-1-(2-pyridyl)-1H-pyrrole;

- 5-[4-(methylsulfonyl)phenyl]-1-(4-methyl-2-pyridyl)-1H-pyrrole;
- 5-[4-(methylsulfonyl)phenyl]-1-(4-methyl-3-pyridyl)-1H-pyrrole;
- 5 5-[4-(methylsulfonyl)phenyl]-1-(5-methyl-2-pyridyl)-1H-pyrrole;
- 5-[4-(methylsulfonyl)phenyl]-1-(5-methyl-3-pyridyl)-1H-pyrrole;
- 5-[4-(methylsulfonyl)phenyl]-1-(3-methyl-2-pyridyl)-1H-pyrrole;
- 10 5-[4-(methylsulfonyl)phenyl]-1-(2-methyl-3-pyridyl)-1H-pyrrole;
- 1-(4-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 15 1-(4-methylthiophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 1-(4-methylsulfinylphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 20 1-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 1-(3-chloro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 25 1-(3,5-dichloro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 1-(3,5-difluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 1-(3-chloro-4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 30 1-(4-hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 1-(4-hydroxymethylphenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 35 1-[4-[5-[4-(aminosulfonyl)phenyl]-1H-pyrrol-1-yl]phenyl]ethanone;

- 4-[1-(4-fluorophenyl)-2-methyl-3-
[(trifluoromethyl)sulfonyl]-1H-pyrrol-5-
yl]benzenesulfonamide;
4-[3-bromo-1-(4-fluorophenyl)-2-methyl-1H-pyrrol-5-
5 yl]benzenesulfonamide;
4-[3-chloro-1-(4-fluorophenyl)-2-methyl-1H-pyrrol-5-
yl]benzenesulfonamide;
4-[1-(4-fluorophenyl)-2-methyl-3-trifluormethyl-1H-
pyrrol-5-yl]benzenesulfonamide;
10 4-[1-(4-fluorophenyl)-2-methyl-3-difluoromethyl-1H-
pyrrol-5-yl]benzenesulfonamide;
2,2,2-trifluoro-1-[1-(4-fluorophenyl)-2-methyl-5-[4-
(aminosulfonyl)phenyl]-1H-pyrrol-3-yl]ethanone;
4-[1-(cyclohexyl)-1H-pyrrol-5-yl]benzenesulfonamide;
15 4-[1-phenyl-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(3,4-difluorophenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;
4-[1-(4-trifluoromethylphenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;
20 4-[1-(4-methylphenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;
4-[1-(4-pyridyl)-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(4-chlorophenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;
25 4-[1-(4-methylthiophenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;
4-[1-(4-methylsulfinylphenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;
4-[1-(4-methoxyphenyl)-1H-pyrrol-5-
30 yl]benzenesulfonamide;
4-[1-(3-fluoro-4-methoxyphenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;
4-[1-(3-chloro-4-methoxyphenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;
35 4-[1-(3,5-dichloro-4-methoxyphenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;
4-[1-(3,5-difluoro-4-methoxyphenyl)-1H-pyrrol-5-
yl]benzenesulfonamide;

- 4-[1-(3-chloro-4-fluorophenyl)-1H-pyrrol-5-yl]benzenesulfonamide;
4-[1-(4-hydroxyphenyl)-1H-pyrrol-5-yl]benzenesulfonamide;
5 4-[1-(4-hydroxymethylphenyl)-1H-pyrrol-5-yl]benzenesulfonamide;
- 1-[4-(methylsulfonyl)phenyl]-5-(4-pyridyl)-1H-pyrrole;
1-[4-(methylsulfonyl)phenyl]-5-(3-pyridyl)-1H-pyrrole;
10 1-[4-(methylsulfonyl)phenyl]-5-(2-pyridyl)-1H-pyrrole;
1-[4-(methylsulfonyl)phenyl]-5-(4-methyl-2-pyridyl)-1H-pyrrole;
1-[4-(methylsulfonyl)phenyl]-5-(4-methyl-3-pyridyl)-1H-pyrrole;
15 1-[4-(methylsulfonyl)phenyl]-5-(5-methyl-2-pyridyl)-1H-pyrrole;
1-[4-(methylsulfonyl)phenyl]-5-(5-methyl-3-pyridyl)-1H-pyrrole;
1-[4-(methylsulfonyl)phenyl]-5-(3-methyl-2-pyridyl)-1H-pyrrole;
20 1-[4-(methylsulfonyl)phenyl]-5-(2-methyl-3-pyridyl)-1H-pyrrole;
5-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
25 5-(4-methylthiophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
5-(4-methylsulfinylphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
5-(4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
30 5-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
5-(3-chloro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
35 5-(3,5-dichloro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
5-(3,5-difluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;

- 5-(3-chloro-4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
5-(4-hydroxyphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
5 5-(4-hydroxymethylphenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
- 5-[4-[1-[4-(aminosulfonyl)phenyl]-1H-pyrrol-1-yl]phenyl]ethanone;
10 4-[5-(cyclohexyl)-1H-pyrrol-1-yl]benzenesulfonamide;
4-[5-phenyl-1H-pyrrol-1-yl]benzenesulfonamide;
4-[5-(3,4-difluorophenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
4-[5-(4-trifluoromethylphenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
15 4-[5-(4-methylphenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
- 4-[5-(4-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
20 4-[5-(3-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
4-[5-(2-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
4-[5-(4-methyl-3-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
4-[5-(4-methyl-2-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
25 4-[5-(5-methyl-3-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
4-[5-(5-methyl-2-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
30 4-[5-(2-methyl-3-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
4-[5-(3-methyl-2-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
4-[1-(4-fluorophenyl)-3-[(trifluoromethyl)sulfonyl]-1H-pyrrol-5-yl]benzenesulfonamide;
35 4-[3-bromo-1-(4-fluorophenyl)-1H-pyrrol-5-yl]benzenesulfonamide;

- 4-[3-chloro-1-(4-fluorophenyl)-1H-pyrrol-5-yl]benzenesulfonamide;
 4-[1-(4-fluorophenyl)-3-trifluormethyl-1H-pyrrol-5-yl]benzenesulfonamide;
 5 4-[1-(4-fluorophenyl)-3-difluoromethyl-1H-pyrrol-5-yl]benzenesulfonamide;
 2,2,2-trifluoro-1-[1-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-1H-pyrrol-3-yl]ethanone;
 4-[5-(4-chlorophenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
 10 4-[5-(4-methylthiophenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
 4-[5-(4-methylsulfinylphenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
 15 4-[5-(4-methoxyphenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
 4-[5-(3-fluoro-4-methoxyphenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
 4-[5-(3-chloro-4-methoxyphenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
 20 4-[5-(3,5-dichloro-4-methoxyphenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
 4-[5-(3-chloro-4-fluorophenyl)-1H-pyrrol-1-yl]benzenesulfonamide;
 25 4-[5-(4-hydroxyphenyl)-1H-pyrrol-1-yl]benzenesulfonamide; and
 4-[5-(4-hydroxymethylphenyl)-1H-pyrrol-1-yl]benzenesulfonamide.

- 30 The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH₂-) radical.
- 35 Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon

atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals

5 having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "halo" means halogens such as fluorine, chlorine,

10 bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical,

15 for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals

20 having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl,

25 dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more

30 hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl,

35 hydroxybutyl and hydroxyhexyl. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy

radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. The term "alkoxyalkyl" also embraces alkyl radicals

5 having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals.

10 Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and methoxypropyl. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to

15 provide "haloalkoxy" or haloalkoxyalkyl radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy,

20 trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having

25 three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces partially saturated carbocyclic radicals having three to twelve carbon atoms. More preferred

30 cycloalkenyl radicals are "lower cycloalkenyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl and cyclohexenyl. The term "aryl", alone or in combination, means a carbocyclic

35 aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl,

tetrahydronaphthyl, indane and biphenyl. Said "aryl" group may have 1 to 3 substituents such as halo, lower alkyl, hydroxy, lower alkoxy, lower alkylcarbonyl and lower haloalkyl. The term

5 "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated

10 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen

15 atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include

20 dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4

25 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl

30 [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl,

35 tetrazolopyridazinyl [e.g., tetrazolo[1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.;

unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl" group may have 1 to 3 substituents such as halo, lower alkyl, hydroxy, oxo, amino and lower alkylamino. More preferred heteroaryl radicals include five to six membered heteroaryl radicals. The term "heteroarylalkyl" embraces heteroaryl-substituted alkyl radicals. More preferred heteroarylalkyl radicals are "lower heteroarylalkyl" radicals having one to six carbon atoms and a heteroaryl radical. Examples include such heteroarylalkyl radicals such as pyridylmethyl and thienylmethyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of

such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces alkylthio radicals attached to an alkyl radical. More preferred

5 alkylthioalkyl radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms and an alkylthio radical as described above. Examples of such radicals include methylthiomethyl. The term "arylthio" embraces radicals containing an

10 aryl radical, attached to a divalent sulfur atom, such as a phenylthio radical. The term "arylthioalkyl" embraces arylthio radicals attached to an alkyl radical. More preferred arylthioalkyl radicals are "lower arylthioalkyl" radicals having

15 alkyl radicals of one to six carbon atoms and an arylthio radical as described above. Examples of such radicals include phenylthiomethyl. The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten

20 carbon atoms, attached to a divalent $-S(=O)-$ radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl,

25 butylsulfinyl and hexylsulfinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where

30 alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl.

35 The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkylsulfonyl" radicals. More preferred

haloalkylsulfonyl radicals are "lower haloalkylsulfonyl" radicals having one or more halo atoms attached to lower alkylsulfonyl radicals as described above. Examples of such lower

5 haloalkylsulfonyl radicals include fluoromethylsulfonyl, trifluoromethylsulfonyl and chloromethylsulfonyl. The term "arylsulfonyl" embraces aryl radicals as defined above, attached to a sulfonyl radical. Examples of such radicals

10 include phenylsulfonyl. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denotes $\text{NH}_2\text{O}_2\text{S}-$. The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include formyl,

15 alkanoyl and aroyl radicals. The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-\text{CO}_2\text{H}$. The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes $-(\text{C}=\text{O})-$. The term

20 "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" embraces alkoxy radicals having one to six carbon atoms. Examples of such

25 "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl

30 radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in said aralkyl may be

35 additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The terms "alkylcarbonyl", "arylcarbonyl" and

"aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, respectively, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred alkylcarbonyl radicals are

5 "lower alkylcarbonyl" radicals having one to six carbon atoms. Examples of such radicals include methylcarbonyl and ethylcarbonyl. More preferred aralkylcarbonyl radicals are "lower aralkylcarbonyl" radicals having aryl radicals attached to alkyl

10 radicals having one to six carbon atoms. Examples of such aralkylcarbonyl radicals include benzylcarbonyl. An example of an arylcarbonyl radical is phenylcarbonyl. The term "alkoxycarbonylalkyl" embraces radicals having

15 "alkoxycarbonyl", as defined above substituted to an alkyl radical. More preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms. Examples of

20 such lower alkoxycarbonylalkyl radicals include methoxycarbonylmethyl. The term "haloalkylcarbonyl" embraces radicals having a haloalkyl radical as described above attached to a carbonyl radical. More preferred radicals are "lower

25 haloalkylcarbonyl" radicals where lower haloalkyl radicals, as described above are attached to a carbonyl radical. The term "carboxyalkyl" embraces radicals having a carboxy radical as defined above, attached to an alkyl radical. More preferred are

30 "lower carboxyalkyl" which embrace lower alkyl radicals as defined above. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl, carboxypropyl and carboxybutyl. The term "heteroaralkyl" embraces heteroaryl-substituted

35 alkyl radicals. More preferred heteroaralkyl radicals are "lower heteroaralkyl" radicals having five to six membered heteroaryl radicals attached to one to six carbon atoms. Examples of such radicals

include pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. Said "aryloxy" group may be optionally substituted with 1 to 3 substituents, such as halo, lower alkyl, hydroxy, lower alkoxy, lower alkylcarbonyl and lower haloalkyl. The term "heteroaryloxy" embraces heteroaryl radicals as defined above attached to an oxygen radical. More preferred heteroaryloxy radicals are "lower heteroaryloxy" radicals having five to six membered heteroaryl radicals. The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces alkyl radicals having one or more aralkoxy radicals attached to the alkyl radical, that is, to form monoaralkyloxyalkyl and diaralkyloxyalkyl radicals. The "aralkoxy" or "aralkoxyalkyl" radicals may be further substituted on the aryl ring portion of the radical. More preferred aralkoxyalkyl radicals are "lower aralkoxyalkyl" having an alkoxy attached to one to six carbon atoms. Examples of lower aralkoxyalkyl radicals include benzyloxymethyl. The term "heteroarylthio" embraces radicals having heteroaryl radicals attached to a sulfur radical. More preferred heteroarylthio radicals are "lower heteroarylthio" radicals having five to six membered heteroaryl radicals. Examples of such radicals include 2-furylthio, 2-thienylthio, 3-thienylthio, 4-pyridylthio and 3-pyridylthio. The term "heteroarylalkylthio" denotes radicals having an heteroaryl radical attached to an alkylthio radical. More preferred heteroarylalkylthio radicals are "lower heteroarylalkylthio" radicals having

heteroaryl radicals attached to lower alkylthio radicals as described above. Examples of such radicals include furylmethylthiomethyl and quinolymethylthioethyl. The term

- 5 "heteroarylalkylthioalkyl" denotes radicals having an heteroaryl radical attached to an alkylthio radical further attached through the sulfur atom to an alkyl radical. More preferred heteroarylalkylthioalkyl are "lower
- 10 heteroarylalkylthioalkyl" radicals having lower heteroarylalkyl radicals as described above. Examples of such radicals include furylmethylthiomethyl and quinolymethylthioethyl. The term "heteroarylthioalkyl" denotes radicals
- 15 having an heteroaryl radical attached to a sulfur atom further attached through the sulfur atom to an alkyl radical. More preferred heteroarylthioalkyl radicals are "lower heteroarylthioalkyl" having lower heteroarylthio radicals as described above.
- 20 Examples of such radicals include thienylthiomethyl and pyridylthiohexyl. The term "aralkylthio" embraces radicals having aralkyl radicals attached to a bridging sulfur atom. More preferred aralkylthio radicals are "lower aralkylthio"
- 25 radicals having the aryl radicals attached to one to six carbon atoms. Examples of such radicals include benzylthio and phenylethylthio. The term "aralkylthioalkyl" embraces radicals having aralkyl radicals attached to alkyl radicals through a
- 30 bridging sulfur atom. More preferred aralkylthioalkyl radicals are "lower aralkylthioalkyl" radicals having the aralkylthio radicals attached to one to six carbon atoms. Examples of such radicals include benzylthiomethyl
- 35 and phenylethylthiomethyl. The term "heteroaryloxyalkyl" denotes radicals having an heteroaryl radical attached to an oxygen atom further attached through the oxygen atom to an alkyl

radical. More preferred heteroaryloxyalkyl radicals are "lower heteroaryloxyalkyl" radicals having five to six membered heteroaryl radicals. Examples of such radicals include furyloxyethyl,

5 pyridyloxymethyl and thienyloxyhexyl. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" having one to six carbon atoms. Examples include aminomethyl,

10 aminoethyl and aminobutyl. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with at least one alkyl radical. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" having one to

15 six carbon atoms attached to a lower aminoalkyl radical as described above. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. The term

20 "alkylamino" denotes amino groups which have been substituted with one or two alkyl radicals. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term

25 "alkylaminocarbonyl" embraces alkylamino radicals, as described above, to a carbonyl radical. More preferred alkylaminocarbonyl radicals are "lower alkylaminocarbonyl" having lower alkylamino radicals, as described above, attached to a carbonyl

30 radical. Examples of such radicals include N-methylaminocarbonyl and N,N-dimethylcarbonyl. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be

35 further substituted on the aryl ring portion of the radical. The terms "N-arylaminoalkyl" and "N-aryl-N-alkylaminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and

one alkyl radical, respectively, and having the amino group attached to an alkyl radical. More preferred arylaminoalkyl radicals are "lower arylaminoalkyl" having the arylamino radical

5 attached to one to six carbon atoms. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$. The term "alkylaminocarbonylalkyl" denotes an

10 alkylaminocarbonyl group which is attached to an alkyl radical. More preferred are "lower alkylaminocarbonylalkyl" having lower alkylaminocarbonyl radicals as described above attached to one to six carbon atoms. The term

15 "aryloxyalkyl" embraces alkyl radicals having one or more aryloxy radicals, aryl radicals attached to a divalent oxygen atom, attached to the alkyl radical, that is, to form monoaryloxyalkyl and diaryloxyalkyl radicals. The more preferred aryloxyalkyl radicals

20 are "lower aryloxyalkyl" radicals having aryloxy radicals attached to one to six carbon atoms. Examples include phenoxymethyl where the phenyl ring is optionally substituted with . The term

"heteroarylalkoxy" embraces radicals having one or

25 more heterocyclic radicals attached to an alkoxy radical. More preferred heteroarylalkoxy radicals are "lower heteroarylalkoxy" radicals having five to six membered heteroaryl radicals. Examples of such radicals include 2-, 3-thienylmethoxy, 2-, 3-

30 furylmethoxy and 2-, 3-, 4-pyridylmethoxy. The term "heteroarylalkoxyalkyl" embraces alkyl radicals having one or more heterocyclic radicals attached to an alkoxy radical, further attached to the alkyl radical. More preferred heteroarylalkoxyalkyl

35 radicals are "lower heteroarylalkoxyalkyl radicals having five to six membered heteroaryl radicals.

Examples of such radicals include 2-thienylmethoxymethyl.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formula I in association with at least one
5 pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating cyclooxygenase-2 mediated disorders, such as inflammation, in a subject, the method
10 comprising treating the subject having such disorder with a therapeutically-effective amount of a compound of Formula I.

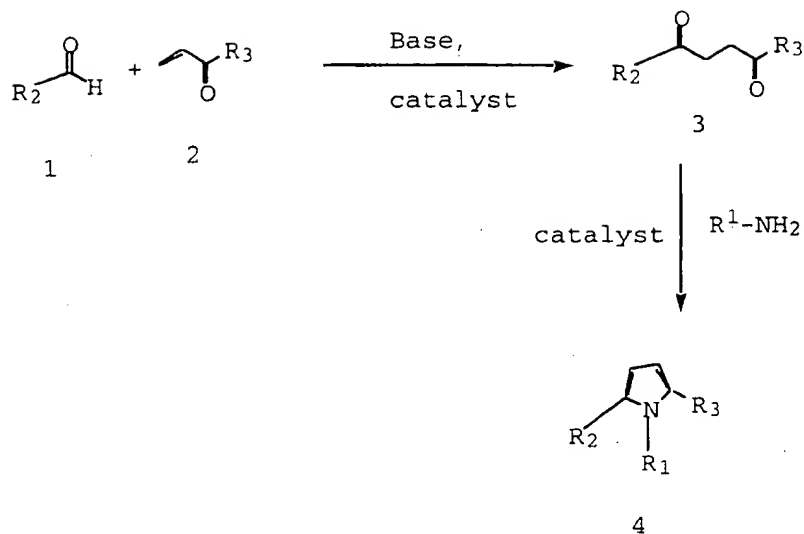
Also included in the family of compounds of Formula I are the pharmaceutically-acceptable salts
15 thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable.
20 Suitable pharmaceutically-acceptable acid addition salts of compounds of Formulas I-III may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric
25 and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic

classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic, methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, stearic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β -hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I-III include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I.

GENERAL SYNTHETIC PROCEDURES

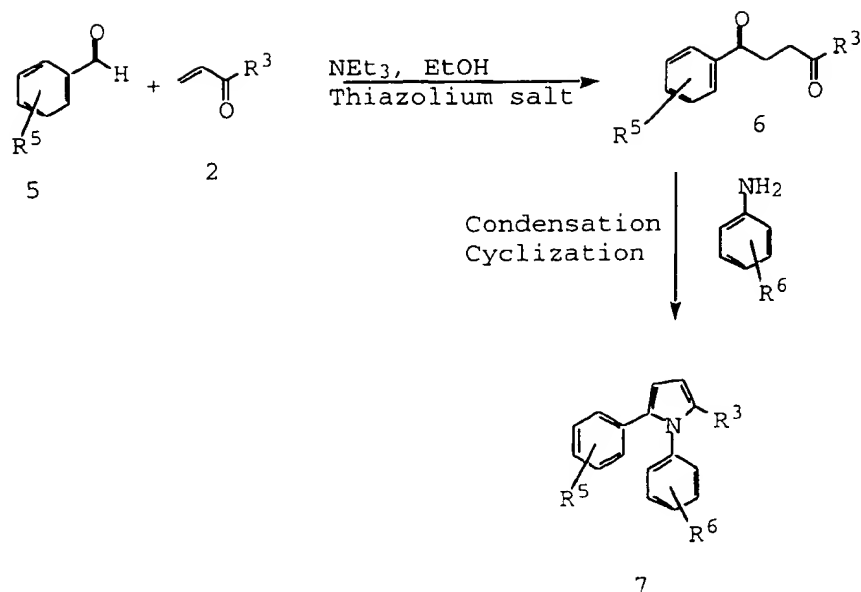
The compounds of the invention can be synthesized according to the following procedures of Schemes I-VII, wherein the R¹-R⁸ substituents are as defined for Formulas I-III, above, except where further noted.

Scheme I



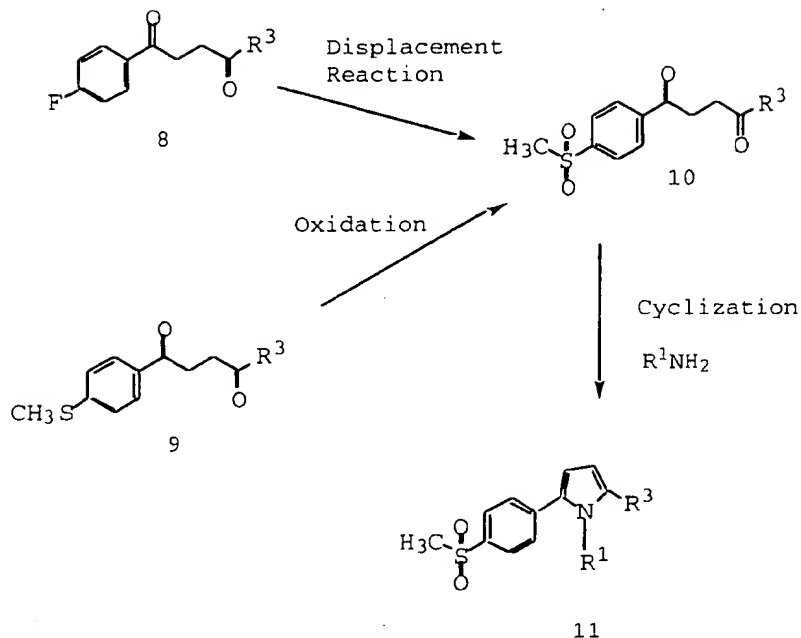
- 5 Scheme I shows the two-step general procedure for
the synthesis of substituted pyrroles 4 of the invention.
In step 1, aldehyde 1 is reacted with α,β -unsaturated
ketones 2 in the presence of a base (such as
triethylamine, diisopropylethylamine, pyridine and the
10 like) to give the 1,4-diketone derivative 3. Suitable
catalysts for this reaction are thiazolium salts or
cyanides (e.g., NaCN, KCN). A variety of catalysts and
conditions suitable for this reaction are discussed in
Angewandte Chemie (Engl.), **15**, 639 (1976) and the
15 references cited therein. In step 2, the 1,4-diketone
intermediate 3 is reacted with amines in the presence of
acid catalysts such as *p*-toluenesulfonic acid to give the
targeted pyrroles 4. Suitable solvents for this reaction
are e. g., toluene, xylene and benzene, with or without
20 the presence of molecular sieves.

Scheme II



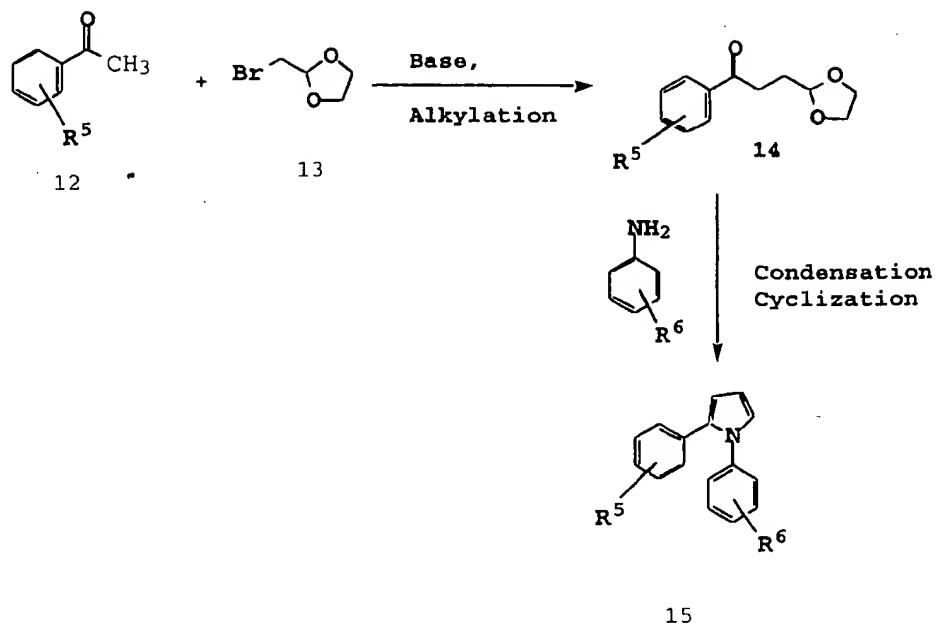
5 Scheme II shows the general procedure for the
 synthesis of 1,2-diphenylpyrroles **7** of the invention. In
 step 1, the substituted benzaldehyde **5** is reacted with
 α,β -unsaturated ketones **2** in the presence of a base to
 give the 1,4-diketone derivative **6**. Suitable catalysts
 10 for this reaction are thiazolium salts or cyanides (e.
 g., $NaCN$, KCN). In step 2, the 1,4-diketone intermediate
6 is reacted with substituted anilines in the presence of
 acid catalysts such as *p*-toluenesulfonic acid to give the
 targeted 1,2-diphenylpyrroles **7**.

Scheme III



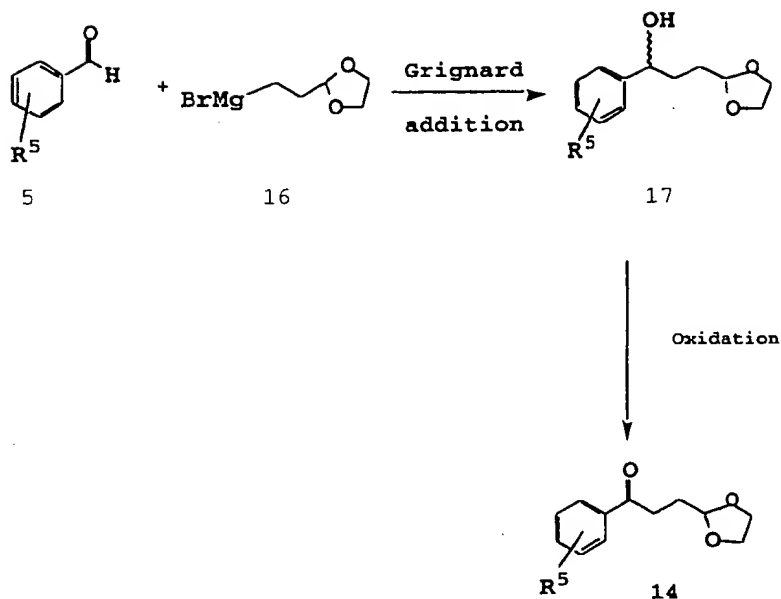
5 Scheme III shows synthesis of substituted pyrroles
11 containing a methylsulfonyl group. The synthesis of
key intermediate **10** can be accomplished by direct
displacement of a fluorine atom, such as with
methanesulfinic acid sodium salt. Suitable solvents for
10 this reaction are, e.g., dimethylformamide, dimethyl
acetamide, dimethyl sulfoxide or 2-pyrrolidinone at
temperature of about 100-140 °C for several hours to
days. Alternately, the intermediate **10** can be synthesized
by oxidation of the corresponding methylthio derivative
15 **9**. This oxidation may be carried with oxidizing agents
such as OXONE® or hydrogen peroxide. The conversion of **10**
to desired substituted pyrroles can be achieved by
condensing with substituted amines **11** as discussed in
step 2, Scheme I.

Scheme IV



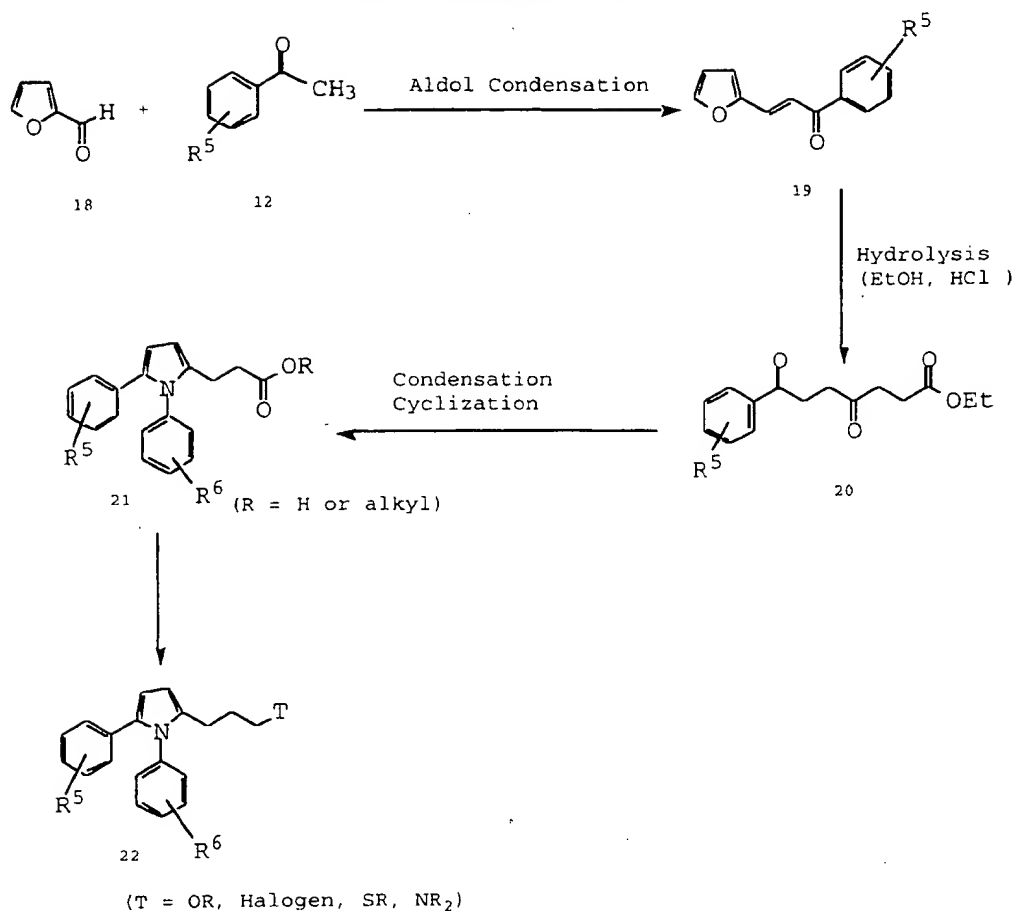
- 5 Scheme IV shows an alternative synthesis of 1,2-diphenylpyrroles **15** wherein R^3 is hydrido. In step 1, the substituted acetophenones **12** are reacted with 2-bromomethyl-1,3-dioxolane **13** to form the protected ketone **14** using a base such as NaH, KH, or potassium *t*-butoxide.
- 10 Suitable solvents for this alkylation reaction include dimethylformamide, dimethylacetamide and dimethylsulfoxide. The reaction may be carried out at about -20 °C to about 50 °C. In step 2, the desired 1,2-diphenylpyrroles **15** can be synthesized by condensing the
- 15 protected ketone **14** with an aniline. The conditions used are similar to those discussed in step 2, Scheme I.

Scheme V



5 Scheme V shows an alternate method of synthesizing
the intermediate **14** of Scheme IV. In step 1, the
substituted benzaldehyde **5** is reacted with Grignard
reagent from 3-bromoethyl-1,3-dioxolane **16** and magnesium
to form the alcohol **17**. This reaction is preferentially
10 carried out in ethereal solvents such as tetrahydrofuran,
diethyl ether, dioxane, dimethoxyethane at temperature of
about $-100-0^{\circ}\text{C}$. In step 2, the oxidation of the alcohol
17 to the desired ketone intermediate **14** can be carried
out using a variety of conditions familiar to those
15 skilled in the art.

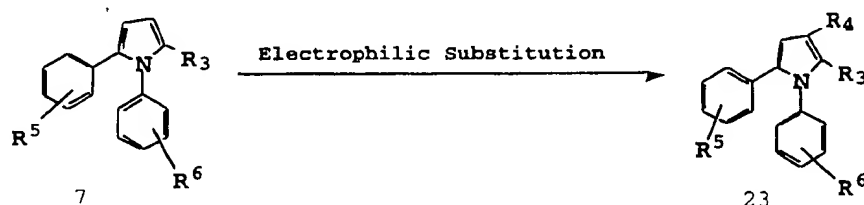
Scheme VI



Scheme VI shows a general synthesis of
 5 diarylpyrroles additionally substituted at position 2 of
 the pyrroles. In step 1, 2-furaldehyde **18** is condensed
 with substituted acetophenone **12** in the presence of a
 base to give the unsaturated intermediate **19**. Suitable
 bases for this reaction are, e.g., sodium methoxide,
 10 sodium (or potassium) *t*-butoxide, triethylamine,
 diisopropylethylamine and the like. In step 2, the furan
 ring is opened under hydrolytic conditions to give the
 intermediate **20**. This reaction is preferably carried out
 in alcoholic solvents using aqueous mineral acids. In
 15 step 3, the intermediate **20** is reacted with substituted
 anilines to give the targeted pyrroles **21**. This reaction
 can be carried out using the conditions suggested in step

2, Scheme 1. In step 4, the carboxylic group is reduced to the alcohol (22, T = OH) and the alcohol is converted to ether (22, T = OR) or other derivatives (22, T = halogen, NR₂, SR). These synthetic transformations can be
 5 achieved using the conditions familiar to those skilled in the art.

Scheme VII



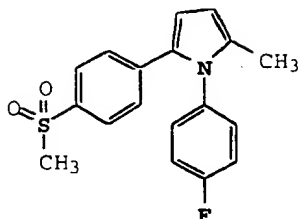
Scheme VII shows a general method for the synthesis
 10 of tetrasubstituted pyrroles 23 from trisubstituted pyrroles 7. A number of substituents such as (R⁴ = halogen, -CHO, -CN, -COR, -SO₂R, -CO₂R, alkyl, aralkyl, etc.) can be synthesized by direct electrophilic substitutions. For example, *N*-bromosuccinimide, *N*-chlorosuccinimide, iodine can be used for introduction of
 15 halogen substituted pyrroles. Dimethylformamide can be used for the synthesis of formyl (R⁴ = CHO) derivatives. The synthesis of acetyl (COR) or alkylsulfonyl (SO₂R) derivatives can be accomplished by using Friedel-Crafts
 20 reaction. The synthesis of compounds with variety of groups (R⁴ = halogen, alkyl, aminoalkyl, alkoxyalkyl, aryl, acyl and the like) can be accomplished by following the literature procedures (see, e.g., *J. Org. Chem.*, **55**, 6317 (1990); *Eur. J. Med. Chem.*, **27**, 701 (1992); *J. Org. Chem.*, **57**, 1653 (1992); *J. Med. Chem.*, **35**, 4813 (1992);
 25 and the references cited therein). Some of the targeted compounds (e.g., R⁴ = alkoxyalkyl, aminoalkyl, mercaptoalkyl, haloalkyl and the like) can also be synthesized by the functional group transformation of
 30 groups such as Br, CHO, CO₂R using the conditions familiar to those skilled in the art.

The following examples contain detailed descriptions of the methods of preparation of

compounds of Formula I-III. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These
5 detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra
10 consistent with their assigned structures. In some cases, the assigned structures were confirmed by nuclear Overhauser effect (NOE) experiments.

The following abbreviations are used:

- 15 HCl - hydrochloric acid
- HBr - hydrobromic acid
- DMSO - dimethylsulfoxide
- MgSO₄ - magnesium sulfate
- Na₂SO₄ - sodium sulfate
- 20 H₂SO₄ - sulfuric acid
- AcOH - acetic acid
- DMF - dimethylformamide
- THF - tetrahydrofuran
- NaOH - sodium hydroxide
- 25 Pt/C - platinum on carbon
- Pd/C - palladium on carbon
- EtOH - ethanol
- NaH - sodium hydride
- KH - potassium hydride
- 30 NaCN - sodium cyanide
- KCN - potassium cyanide
- KBr - potassium bromide
- min - minutes
- h - hours
- 35 OXONE® - potassium peroxymonosulfate

Example 1

5 **1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole**

Step 1: Preparation of 1-[4-(methylthio)phenyl]pentane-1,4-dione.

10 To a solution of 4-(methylthio)benzaldehyde (12 mL, 0.09 mol) in ethanol (30 mL), triethylamine (19.5 mL, 0.14 mol), methyl vinyl ketone (5.8 mL, 0.07 mol) and 3-ethyl-5-(2-hydroxyethyl)-4 methylthiazolium bromide (3.53 g, 0.014 mol) were added. The mixture
15 was heated at 75-80 °C for 20 hours and cooled. The solvent was removed under reduced pressure and the residue was treated with 2N HCl (300 mL). After extraction with methylene chloride, the organic layer was washed with aqueous sodium bicarbonate and water.
20 The organic fractions were dried over MgSO₄, filtered and concentrated to give a crude orange liquid (16.2 g). After chromatography on silica gel (hexane/ethyl acetate, 7/3), the desired compound was isolated as a pale yellow solid (12.3 g, 71%): mp (DSC) 75 °C; IR
25 (KBr) 3410, 3030, 1711, 1680, 1591, 1556, 1491, 1427; MS (EI) 222 (M⁺). Anal. Calc'd for C₁₂H₁₄SO₂: C, 64.84; H, 6.35. Found: C, 64.65; H, 6.33.

30 Step 2: Preparation of 1-(4-methylsulfonylphenyl)-1,4-pentanedione

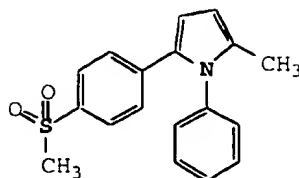
-----To a solution of 1-(4-methylthiophenyl)-1,4-pentanedione (7.8 g, 35 mmol) in methanol (150 mL),

Oxone® (37.7 g, 61.4 mmol) was dissolved in water (150 mL) and added over 5 minutes. After stirring at 25 °C for 2 hours, the reaction mixture was diluted with water (400 mL) and extracted with methylene chloride (3 x 400 mL). The organic layer was washed with brine (200 mL), water (200 mL) and dried (MgSO₄). After filtration and concentration, the crude material was purified by chromatography (silica gel, hexane/ethyl acetate, 3/1) to give 1-(4-methylsulfonylphenyl)-1,4-pentanedione (8.0 g, 91%) as a white crystalline compound: mp (DSC) 138 °C; IR (KBr) 3435, 3098, 3003, 1944, 1713, 1686, 1593, 1572, 1406; MS (DCI, NH₃-PCI) 255 (MH⁺). Anal Calc'd. for C₁₂H₁₄SO₄: C, 56.68; H, 5.55. Found: C, 56.60; H, 5.78.

15

Step 3: Preparation of 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole

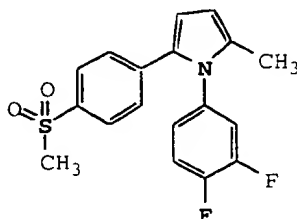
A mixture of 1-(4-methylsulfonylphenyl)-1,4-pentanedione (580 mg, 2.28 mmol) of Step 2, 4-fluoroaniline (0.24 ml, 2.5 mmol) and *p*-toluenesulfonic acid (30 mg) in toluene (50 ml) was heated to reflux for 20 hours. The reaction mixture was cooled, filtered and concentrated. The crude mixture (820 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3) to give 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole (595 mg, 79%) as a white solid: mp (DSC) 157 °C. Anal Calc'd. for C₁₈H₁₆NSO₂F: C, 65.64; H, 4.90; N, 4.25; S, 9.73. Found: C, 65.44; H, 5.05; N, 4.16; S, 9.90.

Example 2

5 **2-Methyl-5-[4-(methanesulfonyl)phenyl]-1-phenyl-1H-pyrrole**

A mixture of 1-(4-methanesulfonylphenyl)-1,4-pentanedione (Example 1, step 2) (300 mg, 1.18 mmol),
10 aniline (0.12 ml, 1.3 mmol) and *p*-toluenesulfonic acid (25 mg) in toluene (50 ml) was heated to reflux for 20 hours. The reaction mixture was cooled, filtered and concentrated. The crude brownish solid (420 mg) was purified by chromatography (silica gel, hexane/ethyl
15 acetate, 7/3) to give 2-methyl-5-[4-(methanesulfonyl)phenyl]-1-phenyl-1H-pyrrole (305 mg, 83%) as a white solid: mp (DSC) 148 °C. Anal Calc'd. for C₁₈H₁₇NSO₂: C, 69.43; H, 5.50; N, 4.50; S, 10.30. Found: C, 69.18; H, 5.42; N, 4.42; S, 10.06.

20

Example 3

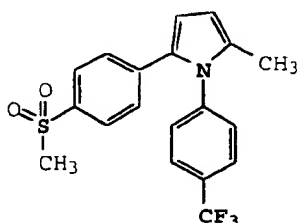
25

1-(3,4-Difluorophenyl)-2-methyl-5-[4-(methanesulfonyl)phenyl]-1H-pyrrole

A mixture of 1-(4-methylsulfonylphenyl)-1,4-pentanedione (Example 1, Step 2) (300 mg, 1.18 mmol), 3,4-difluoroaniline (0.13 ml, 1.3 mmol) and *p*-toluenesulfonic acid (25 mg) in toluene (80 ml) was heated to reflux for 24 hours. The reaction mixture was cooled, filtered and concentrated. The crude dark orange solid (700 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3) to give 1-(3,4-difluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole (370 mg, 90%) as a white solid: mp (DSC) 151 °C. Anal Calc'd. for $C_{18}H_{15}NSO_2F_2$: C, 62.24; H, 4.35; N, 4.03. Found: C, 62.08; H, 4.52; N, 4.05.

15

Example 4



20

2-Methyl-5-[4-(methylsulfonyl)phenyl]-1-[4-(trifluoromethyl)phenyl]-1H-pyrrole

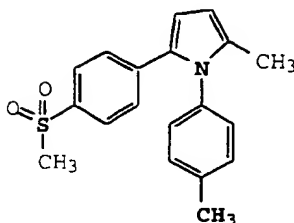
A mixture of 1-(4-methylsulfonylphenyl)-1,4-pentanedione (Example 1, Step 2) (300 mg, 1.18 mmol), 4-(trifluoromethyl)aniline hydrochloride (257 mg, 1.3 mmol) and *p*-toluenesulfonic acid (30 mg) in toluene (80 ml) was heated to reflux for 20 hours. The reaction mixture was cooled, filtered and concentrated. The crude solid (560 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3) to give 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-[4-(trifluoromethyl)phenyl]-1H-pyrrole (351 mg, 78%) as a white solid: mp (DSC) 130 °C. Anal Calc'd. for

48

$C_{19}H_{16}NSO_2F_3$: C, 60.15; H, 4.25; N, 3.69. Found: C, 60.38; H, 4.44; N, 3.67.

Example 5

5



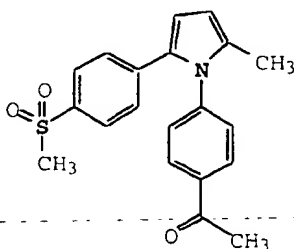
2-Methyl-1-(4-methylphenyl)-5-[4-(methanesulfonyl)phenyl]-1H-pyrrole

10

A mixture of 1-(4-methanesulfonylphenyl)-1,4-pentanedione (Example 1, Step 2) (335 mg, 1.32 mmol), *p*-toluidine (156 mg, 1.45 mmol) and *p*-toluenesulfonic acid (25 mg) in toluene (100 ml) was heated to reflux for 20 hours. The reaction mixture was cooled, filtered and concentrated. The crude solid (560 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3) to give 2-methyl-1-(4-methylphenyl)-5-[4-(methanesulfonyl)phenyl]-1H-pyrrole (390 mg, 91%) as a white solid; mp (DSC) 144 °C. Anal Calc'd. for $C_{19}H_{19}NSO_2$: C, 70.13; H, 5.88; N, 4.30; S, 9.85. Found: C, 69.99; H, 6.23; N, 4.18; S, 9.74.

25

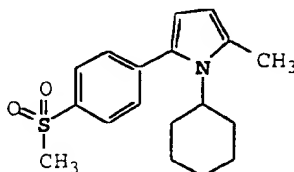
Example 6



1-[4-[2-Methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-1-yl]phenyl]ethanone

A mixture of 1-(4-methylsulfonylphenyl)-1,4-pentanedione (Example 1, Step 2) (400 mg, 1.57 mmol), *p*-amino-acetophenone (234 mg, 1.73 mmol) and *p*-toluenesulfonic acid (30 mg) in toluene (40 ml) was heated to reflux for 5 hours. The reaction mixture was cooled, filtered and concentrated. The crude reddish solid (1.2 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4) to give 1-[4-[2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-1-yl]phenyl]ethanone (336 mg, 61%) as a white solid: mp 179-80 °C. Anal Calc'd. for C₂₀H₁₉NSO₃·0.1 H₂O: C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.68; H, 5.52; N, 3.82; S, 8.08.

Example 7



1-Cyclohexyl-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole

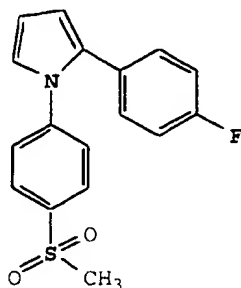
A mixture of 1-(4-methylsulfonylphenyl)-1,4-pentanedione (Example 1, Step 2) (820 mg, 3.23 mmol), cyclohexylamine (410 µl, 3.55 mmol) and *p*-toluenesulfonic acid (50 mg) in toluene (75 ml) was heated to reflux for 24 hours. The reaction mixture was cooled, filtered and concentrated. The crude solid (1.14 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 1/1) to give 1-cyclohexyl-2-

50

methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole (350 mg, 36%) as a white solid: mp (DSC) 141 °C. Anal Calc'd. for C₁₈H₂₃NSO₂: C, 68.10; H, 7.30; N, 4.41; S, 10.10. Found: C, 68.22; H, 7.25; N, 4.30; S, 10.16.

5

Example 8



10 2-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole

Step 1: Preparation of α -(4-fluorophenyl)-1,3-dioxolane-2-propan-3-ol

15 A solution of 2-(2-bromoethyl)-1,3-dioxolane (1.76 ml, 15 mmol) in THF (10 ml) was added over 10 minutes to a suspension of magnesium turnings (410 mg, 16.5 mmol) in THF (10 ml). After stirring for 20 minutes, the reaction mixture was cooled to -70 °C and
20 a solution of 4-fluorobenzaldehyde (1.07 ml, 10 mmol) in THF (10 ml) was added over 10 minutes. The reaction mixture was stirred at -70 °C for 2 hours and quenched with aqueous ammonium chloride. The reaction solution was warmed to room temperature and extracted with
25 ethyl acetate. The organic layer was washed with brine, dried (MgSO₄), filtered and concentrated. The crude was obtained as a white liquid (2.54 g) and purified by chromatography (silica gel, hexane/ethyl acetate, 7/3) to give α -(4-fluorophenyl)-1,3-
30 dioxolane-2-propan-3-ol as a white oil (1.88 g, 83%):

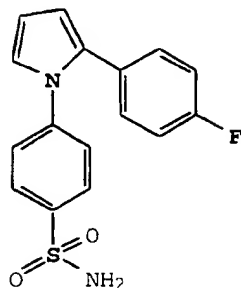
Anal Calc'd. for $C_{12}H_{15}FO_3 \cdot 0.2 H_2O$: C, 62.71; H, 6.75.
Found: C, 62.73; H, 6.64.

5 Step 2: Preparation of 3-(1,3-dioxolan-2-yl)-1-(4-fluorophenyl)propan-1-one

To a solution of α -(4-fluorophenyl)-1,3-dioxolane-2-propan-3-ol (Step 1) (1.75 g, 7.74 mmol) in methylene chloride (100 ml), pyridinium chlorochromate (2.5 g, 11.6 mmol) was added. After
10 stirring at room temperature for 3 hours, the mixture was diluted with ether and filtered through a short silica gel column. The column was eluted with ether and the fractions were combined and concentrated to give the ketone as a white solid (1.69 g, 96%): mp
15 (DSC) 143 °C. Anal Calc'd. for $C_{12}H_{13}FO_3$: C, 64.28; H, 5.84. Found: C, 64.85; H, 6.05.

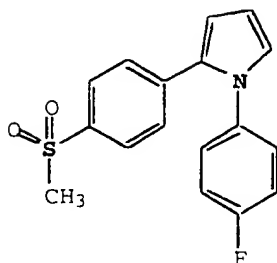
Step 3: Preparation of 2-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole

20 A mixture of the ketone (Step 2) (448 mg, 2 mmol), 4-(methylsulfonyl)aniline (380 mg, 2.2 mmol) and *p*-toluenesulfonic acid (30 mg) in toluene (40 ml) was heated to reflux for 18 hours. The reaction was cooled, filtered and concentrated. The crude solid
25 (750 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 1/1) to give 2-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole (310 mg, 55%) as a white solid: mp (DSC) 201 °C. Anal Calc'd. for $C_{17}H_{14}NSFO_2 \cdot 0.2 H_2O$: C, 64.01; H, 4.55; N, 4.39; S,
30 10.05. Found: C, 64.18; H, 4.33; N, 4.32; S, 10.36.

Example 9

5 **4-[2-(4-Fluorophenyl)-1H-pyrrol-1-yl]benzenesulfonamide**

A mixture of 3-(1,3-dioxolan-2-yl)-1-(4-fluorophenyl)propan-1-one (Example 8, Step 2) (1.6 g, 7.14 mmol), sulfanilamide (1.35 g, 7.86 mmol), *p*-toluenesulfonic acid (120 mg) and molecular sieves (4Å, 3 g) in toluene (250 ml) was heated to reflux for 98 hours. The reaction was cooled, filtered and concentrated. The crude brownish solid (3.2 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4) to give 4-[2-(4-fluorophenyl)-1H-pyrrol-1-yl]benzenesulfonamide (920 mg, 40%) as a white solid: mp (DSC) 206 °C. Anal Calc'd. for C₁₆H₁₃N₂SFO₂·0.2 H₂O: C, 60.06; H, 4.22; N, 8.76; S, 10.02. Found: C, 60.13; H, 4.21; N, 8.61; S, 10.15.

Example 10

5 **1-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-**
 pyrrole

Step 1: Preparation of 5,5-dimethyl-1,3-dioxane-2-
10 propan-3-ol

5,5-Dimethyl-1,3-dioxane-2-propan-3-ol was synthesized by following the literature procedure [J. Org. Chem., **57**, 2195 (1992)].

15 Step 2: Preparation of 5,5-dimethyl-1,3-dioxane-2-
 propanal

To a cold solution of oxalyl chloride (5.5 ml, 63.2 mmol) in methylene chloride (25 ml) at -78 °C, DMSO (10.2 ml, 0.14 mol) was injected in over 5 minutes. After stirring for 15 minutes, a solution of
20 5,5-dimethyl-1,3-dioxane-2-propan-3-ol (Step 1) (10 g, 57.5 mmol) in methylene chloride (100 ml) was added. The reaction solution was stirred for 1 hour and triethylamine (40 ml, 0.2 mol) was added. After stirring at -70 °C for 1 hour, the reaction mixture
25 was warmed to room temperature and stirred for 2 hours. The reaction was quenched with water and extracted with methylene chloride. The organic fractions were washed with aqueous sodium bicarbonate and brine. After drying (Na₂SO₄), filtration and
30 concentration, the crude was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3)

to give 5,5-dimethyl-1,3-dioxane-2-propanal (6.1 g, 61%) as a colorless liquid: Anal Calc'd. for $C_9H_{16}O_3 \cdot 0.2 H_2O$: C, 61.48; H, 9.40. Found: C, 61.46; H, 9.24.

5

Step 3: Preparation of 3-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4-fluorophenyl)propan-1-ol

To a cold solution of 5,5-dimethyl-1,3-dioxane-2-propanal (2 g, 11.62 mmol) (Step 2) at $-70^\circ C$ in THF
10 (50 ml), 4-fluorophenyl magnesium bromide (8.7 ml, 2M solution in ether, 17.44 mmol) was added. After stirring at $-70^\circ C$ for 2 hours, the mixture was warmed to room temperature and stirred overnight. The
15 reaction was quenched with water and extracted with ethyl acetate. The organic fractions were combined and washed successively with water and brine. After drying ($MgSO_4$), filtration and concentration, the crude
20 compound (3.5 g) was purified by chromatography to give 3-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4-fluorophenyl)propan-1-ol (2.73 g) as a white solid: mp (DSC) $84^\circ C$. Anal Calc'd. for $C_{15}H_{21}FO_3$: C, 67.14; H, 7.89. Found: C, 67.18; H, 7.98.

Step 4: Preparation of 3-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4-fluorophenyl)propan-1-one

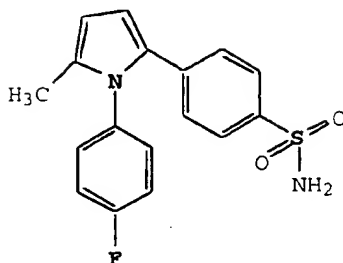
To a solution of 3-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4-fluorophenyl)propan-1-ol (Step 3) (2.6 g, 10.7 mmol) in methylene chloride (100 ml), pyridinium chlorochromate (3.5 g, 16.05 mmol) was added. After
30 stirring at room temperature for 3 hours, the reaction mixture was diluted with ether and filtered through a short silica gel column. The column was eluted with ether and the fractions containing the ketone were combined and concentrated (2.2 g, 85%): mp (DSC) $65^\circ C$. Anal Calc'd. for $C_{15}H_{19}FO_3$: C, 67.65; H, 7.19.
35 Found: C, 67.21; H, 7.43.

Step 5: Preparation of 3-(5,5-dimethyl-1,3-dioxan-2-yl)-1-[4-(methylsulfonyl)phenyl]propan-1-one

To a solution of 3-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4-fluorophenyl)propan-1-one (Step 4) (1.68 g, 6.3 mmol) in dimethylformamide (75 ml), methanesulfinic acid sodium salt (2.9 g, 28.4 mmol) was added. The reaction mixture was heated at 120-30 °C for 72 hours. After cooling, the solvent was removed under reduced pressure and the reaction mixture was diluted with water. The material was extracted with methylene chloride and washed with brine. After drying (MgSO₄), filtration and concentration, the crude solid (2.78 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4) to give the sulfone (1.62 g, 79%) as a white solid: mp (DSC) 104 °C. Anal Calc'd. for C₁₆H₂₂SO₅: C, 58.88; H, 6.79; S, 9.82. Found: C, 58.76; H, 7.01; S, 10.21.

Step 6: Preparation of 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-pyrrole

A mixture of 3-(5,5-dimethyl-1,3-dioxan-2-yl)-1-[4-(methylsulfonyl)phenyl]propan-1-one (Step 5), (1.6 g, 4.9 mmol), 4-fluoroaniline (510 µl, 5.4 mmol) and p-toluenesulfonic acid (120 mg) in toluene (200 ml) was heated to reflux for 72 hours. The reaction mixture was cooled, filtered and concentrated. The crude solid (2.48 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4) to give 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]-1H-pyrrole (695 mg, 45%) as a white solid: mp (DSC) 163 °C. Anal Calc'd. for C₁₇H₁₄NSFO₂: C, 64.75; H, 4.47; N, 4.44. Found: C, 64.71; H, 4.53; N, 4.43.

Example 11

5 **4-[1-(4-Fluorophenyl)-5-methyl-1H-pyrrol-2-yl]benzenesulfonamide**

Step 1: Preparation of 4-(aminosulfonyl)benzoic acid

To a solution of 4-(chlorosulfonyl)benzoic acid
10 (25 g, 0.11 mol) in ether (1.2 L), ammonium hydroxide
(36 ml) was added. After stirring at room temperature
for 5 hours, the solvent was removed and the residue
was stirred with 3N HCl (1 L) for 80 minutes and
filtered. The solid obtained was washed with water (2
15 x 20 ml) and with ether (3 x 20 ml), and dried under
reduced pressure at 80 °C. After concentration, the
white solid obtained (22 g, 97%) was used in the next
step without further purification: mp 279-81 °C. Anal
Calc'd. for C₇H₇NSO₄: C, 41.79; H, 3.51; N, 6.46; S,
20 15.99. Found: C, 41.90; H, 3.45; N, 6.98; S, 15.75.

Step 2: Preparation of methyl [4-(aminosulfonyl)]benzoate

To a solution of 4-(aminosulfonyl)benzoic acid
25 (16 g, 79.6 mmol) (Step 1) in methanol (600 ml), conc.
H₂SO₄ (1.2 ml) was added and the mixture was heated at
reflux for 4 days. The solvent was removed and washed
with ether. The white solid (16.5 g, 96%) was used in
the next reaction without further purification.

Step 3: Preparation of 4-(hydroxymethyl)benzenesulfonamide

To a solution of methyl [4-(aminosulfonyl)]benzoate (5.8 g, 27 mmol) (Step 2) in
5 THF (400 ml), methanol (1.6 ml, 40 mmol) and lithium borohydride (20 ml, 2M solution in THF, 42 mmol) were added over 10 minutes. After heating at reflux for 3.5 hours, the reaction mixture was cooled and poured over ice containing 1N HCl (80 ml). The reaction mixture
10 was extracted with ethyl acetate, dried (Na₂SO₄), filtered and concentrated. The crude mixture was purified by chromatography (silica gel, hexane/ethyl acetate, 1/1) to give 4-(hydroxymethyl)benzenesulfonamide (3.8 g, 75%) as a
15 white solid.

Step 4: Preparation of 4-(formyl)benzenesulfonamide

To a solution of 4-(hydroxymethyl)benzenesulfonamide (Step 3) (3.75 g, 20
20 mmol) in a mixture of acetone (250 ml) and methylene chloride (250 ml), pyridinium chlorochromate (6.47 g, 30 mmol) was added. After stirring at room temperature for 5 hours, the reaction mixture was diluted with ether and filtered through a short silica gel column.
25 The column was eluted with hexane/ethyl acetate, (1/1). The fractions containing the desired material were combined and concentrated to give a white solid (2.0 g, 53%): mp 104-106 °C. Anal Calc'd. for C₇H₇NSO₃: C, 45.40; H, 3.81; N, 7.56; S, 17.31. Found: C, 45.61;
30 H, 3.59; N, 7.18; S, 16.27.

Step 5: Preparation of 4-(1,3-dioxopentyl)benzenesulfonamide

To a solution of 4-(formyl)benzenesulfonamide
35 (Step 4) (900 mg, 4.8 mol) in DMF (10 ml), sodium cyanide (23.5 mg, 0.48 mmol) in DMF (20 ml) was added. After stirring for 5 minutes, a solution of methyl

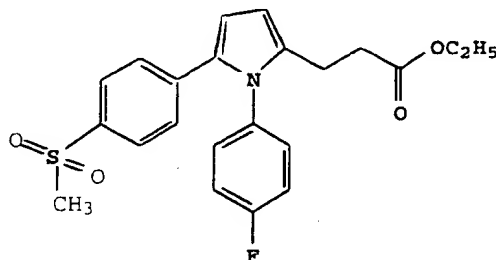
58

vinyl ketone (0.4 ml, 4.8 mmol) in DMF (15 ml) was added. After stirring at room temperature for 20 hours, the reaction mixture was diluted with water and extracted with methylene chloride. The organic fractions were combined, washed with brine, dried (Na₂SO₄), filtered and concentrated. The crude was purified by chromatography on silica gel (hexane/ethyl acetate, 3/1) to give the desired compound as a white solid (180 mg, 15%).

Step 6: Preparation of 4-[1-[4-fluorophenyl]-5-methyl-1H-pyrrol-2-yl]benzenesulfonamide

A mixture of 4-(1,3-dioxopentyl)benzenesulfonamide (160 mg, 0.63 mmol) of (Step 5), 4-fluoroaniline (65 μ l, 0.69 mmol) and *p*-toluenesulfonic acid (6.7 mg) in toluene (25 ml) was heated at reflux for 20 hours. The reaction mixture was cooled, filtered and concentrated. The crude mixture (820 mg) was purified by chromatography (silica gel, toluene/ethyl acetate, 8/2) to give 4-[1-(4-fluorophenyl)-5-methyl-1H-pyrrol-2-yl]benzenesulfonamide (92 mg, 45%) as a white solid: mp 147-48 °C. Anal Calc'd. for C₁₇H₁₅N₂FSO₂: C, 61.14; H, 4.65; N, 8.39; S, 9.60. Found: C, 61.34; H, 4.70; N, 8.21; S, 9.63.

Example 12



Ethyl 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-2-propanoate

Step 1: Preparation of 1-(4-fluorophenyl)-3-(2-furanyl)propan-1-one

To a solution of 2-furaldehyde (4.15 ml, 50 mmol) and 4-fluoroacetophenone (6.16 ml, 50 mmol) in methanol (200 ml), sodium methoxide (2.85 g, 50 mmol) was added. After stirring at room temperature for 18 hours, the reaction mixture was concentrated, resuspended in ethyl acetate (600 ml) and diluted with water. The organic layer was separated, washed with brine, dried (MgSO₄), filtered and concentrated. The crude solid (10.27 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3) to give 1-(4-fluorophenyl)-3-(2-furanyl)propan-1-one (8.9 g, 95%) as a white solid: mp (DSC) 72 °C. Anal Calc'd. for C₁₃H₁₀FO: C, 72.22; H, 4.20. Found: C, 72.18; H, 4.38.

Step 2: Preparation of ethyl 4-fluoro-γζ-dioxobenzeneheptanoate

A solution of ethyl 1-(4-fluorophenyl)-3-(2-furanyl)propan-1-one (Step 1) (7.2 g, 33.3 mmol) in ethanol (200 ml) and conc. HCl (40 ml) was heated at 80-85 °C for 72 hours. The solvent was removed under reduced pressure and redissolved in methylene chloride. The organic layer was separated and concentrated to give a black solid (16.8 g). Chromatography (silica gel, hex/ethyl acetate, 1/1) gave ethyl 4-fluoro-γζ-dioxobenzeneheptanoate (3.9 g, 41%) as a white solid: mp (DSC) 73 °C. Anal Calc'd. for C₁₅H₁₇FO₄: C, 64.28; H, 6.11. Found: C, 64.50; H, 5.89.

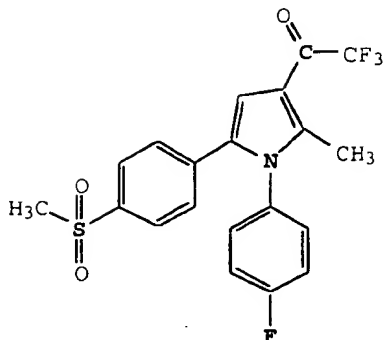
Step 3: Preparation of ethyl 4-(methylsulfonyl)-γζ-dioxobenzeneheptanoate

To a solution of ethyl 4-fluoro-γζ-dioxobenzeneheptanoate (Step 2) (870 mg, 3.1 mmol) in DMF (25 ml), methanesulfinic acid sodium (1.27 g, 12.4

mmol) was added. The reaction mixture was heated at 130-35 °C for 30 hours. After cooling, the solvent was removed under reduced pressure and the reaction mixture was diluted with water. The material was
5 extracted with ethyl acetate and washed with brine. After drying (MgSO₄), filtration and concentration, the crude dark brown solid (840 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 1/1) to give the sulfone (270 mg, 26%) as a white solid: mp
10 (DSC) 97 °C. Anal Calc'd. for C₁₆H₂₀SO₆: C, 56.46; H, 5.92; S, 9.42. Found: C, 56.56; H, 6.10; S, 9.62.

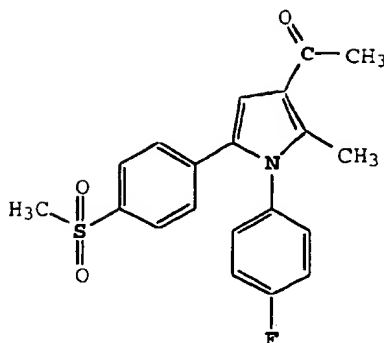
Step 4: Preparation of ethyl 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-2-propanoate

15 A mixture of ethyl 4-(methylsulfonyl)-γ,γ-dioxobenzeneheptanoate (Step 3), (270 mg, 0.79 mmol), 4-fluoroaniline (83 μl, 0.87 mmol) and *p*-toluenesulfonic acid (25 mg) in toluene (40 ml) was heated at reflux for 24 hours. The reaction mixture
20 was cooled, filtered and concentrated. The crude solid (360 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 1/1) to give ethyl 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-2-propanoate (246 mg, 75%) as a white solid: mp (DSC)
25 134 °C. Anal Calc'd. for C₂₂H₂₂NSFO₄: C, 63.60; H, 5.34; N, 3.37; S, 7.72. Found: C, 63.29; H, 5.51; N, 3.38; S, 8.05.

Example 13

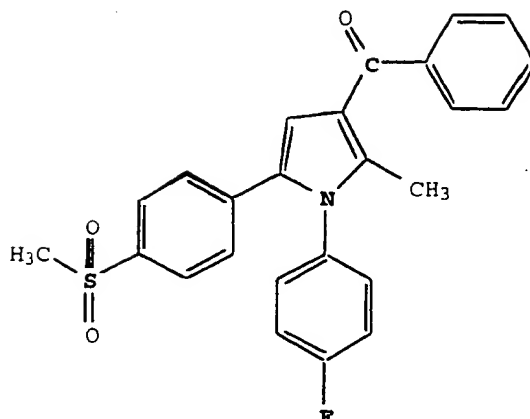
5 **2,2,2-Trifluoro-1-[1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]ethanone**

To a solution of 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole (Example 1) (800
10 mg, 2.43 mmol) in trifluoroacetic acid (7 ml),
trifluoroacetic anhydride (0.7 ml, 4.86 mmol) was
added and the mixture was heated at 50 °C for 3 hours.
The reaction mixture was poured over ice and
neutralized with dilute ammonium hydroxide to pH ~9.
15 After extraction with ethyl acetate, the organic layer
was washed successively with water and brine. The
organic fractions were dried (MgSO₄), filtered and
concentrated. The pale yellow crude solid (1.02 g) was
purified by chromatography (silica gel, hexane/ethyl
20 acetate, 7/3) to give 2,2,2-trifluoro-1-[1-(4-
fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-
1H-pyrrol-3-yl]ethanone (800 mg, 77%) as a white
solid: mp (DSC) 196 °C. Anal Calc'd. for
C₂₀H₁₅NSF₄O₃·0.5 H₂O: C, 55.30; H, 3.71; N, 3.22.
25 Found: C, 55.55, H, 3.79; N, 3.20.

Example 14

5 **1-[1-(4-Fluorophenyl)-2-methyl-5-[4-(methanesulfonyl)phenyl]-1H-pyrrol-3-yl]ethanone**

Acetyl chloride (120 μ l, 1.67 mmol) was slowly added to a stirred slurry of aluminum chloride (223 mg, 1.67 mmol) in methylene chloride (15 ml) at -5 °C. After 30 minutes, a solution 1-(4-fluorophenyl)-2-methyl-5-[4-(methanesulfonyl)phenyl]-1H-pyrrole (Example 1) (500 mg, 1.52 mmol) in methylene chloride (20 ml) was added. The reaction mixture was warmed to room temperature and stirred for 18 hours. The reaction mixture was poured over ice-water and extracted with methylene chloride. The organic fraction was washed with brine, dried (MgSO₄), filtered and concentrated. The crude yellowish solid (570 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4) to give 1-[1-(4-fluorophenyl)-2-methyl-5-[4-(methanesulfonyl)phenyl]-1H-pyrrol-3-yl]ethanone (170 mg, 30%) as a white solid: mp (DSC) 211 °C. Anal Calc'd. for C₂₀H₁₈NSFO₃·0.25 H₂O: C, 63.90; H, 4.96; N, 3.75. Found: C, 63.96; H, 5.04; N, 3.65.

Example 15

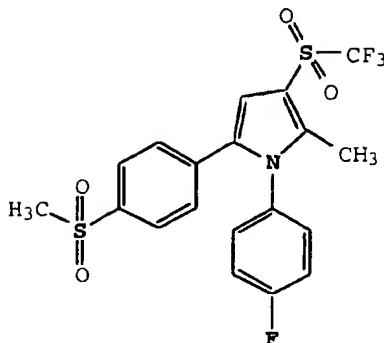
5 **[1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]-phenylmethanone**

10 Benzoyl chloride (180 μ l, 1.52 mmol) was slowly added to a stirred slurry of aluminum chloride (223 mg, 1.67 mmol) in methylene chloride (15 ml) at -10 °C. After 30 minutes, a solution of 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole (Example 1) (500 mg, 1.52 mmol) in

15 methylene chloride (10 ml) was added. The reaction mixture was warmed to room temperature and stirred for 20 hours. The reaction mixture was poured over ice-water and extracted with methylene chloride. The organic fraction was washed with brine, dried (MgSO_4),

20 filtered and concentrated. The crude yellowish solid (570 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4) to give [1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]-phenylmethanone (54 mg, 8%) as a white

25 solid: Anal Calc'd. for $\text{C}_{25}\text{H}_{20}\text{NSFO}_3 \cdot 0.5 \text{H}_2\text{O}$: C, 67.86; H, 4.78; N, 3.17. Found: C, 67.59; H, 4.70; N, 3.07.

Example 16

5

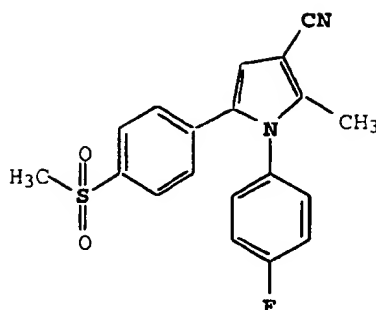
1-(4-Fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-3-[(trifluoromethyl)sulfonyl]-1H-pyrrole

10 To a solution of 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole (Example 1) (2.5 g, 7.6 mmol) in methylene chloride (100 ml) at 0 °C, aluminum chloride (1.15 g, 8.36 mmol) and trifluoromethanesulfonic anhydride (2 ml, 11.8 mmol)

15 were added. After 30 minutes, the reaction mixture was warmed to room temperature and heated at reflux for 48 hours. The reddish orange reaction mixture was cooled, poured over ice-water and extracted with methylene chloride. The organic fractions were washed with

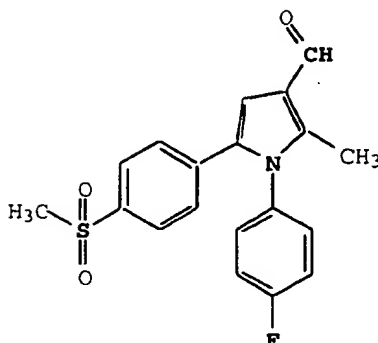
20 brine, dried (MgSO₄), filtered and concentrated. The crude orange solid (3.2 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3) to give 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-3-[(trifluoromethyl)sulfonyl]-

25 1H-pyrrole (248 mg, 7%) as a white solid: mp 162-64 °C. Anal Calc'd. for C₁₉H₁₅NS₂F₄O₄: C, 49.45; H, 3.28; N, 3.04. Found: C, 49.46; H, 3.34; N, 2.95.

Example 17

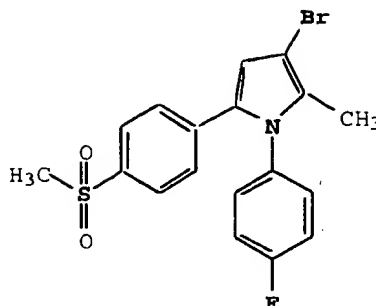
5 **1-(4-Fluorophenyl)-2-methyl-5-[4-**
 (methylsulfonyl)phenyl]-1H-pyrrole-3-carbonitrile

To a cold solution of 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole
10 (Example 1) (750 mg, 2.28 mmol) in DMF (8 ml) and acetonitrile (8 ml) at -78 °C, chlorosulfonyl
isocyanate (200 µl, 2.28 mmol) was added. The reaction mixture was warmed to 20 °C over 4 hours, quenched by
adding excess of water, and extracted with ethyl
15 acetate. The organic fractions were washed with brine, dried (MgSO₄), filtered and concentrated. The crude
colorless liquid (0.77 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 6/4)
to give 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-3-carbonitrile (620
20 mg, 77%) as a white solid: mp (DSC) 205 °C. Anal
Calc'd. for C₁₉H₁₅N₂SFO₂: C, 64.39; H, 4.27; N, 7.90.
Found: C, 64.11; H, 4.45; N, 7.60.

Example 18

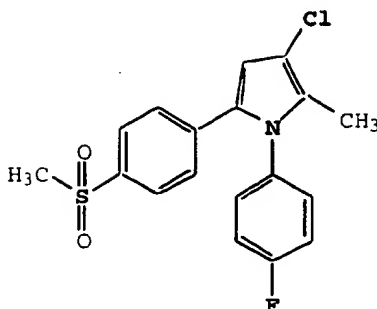
5 **1-(4-Fluorophenyl)-2-methyl-5-[4-**
 (methylsulfonyl)phenyl]-1H-pyrrole-3-carboxaldehyde

To a solution of 1-(4-fluorophenyl)-2-methyl-5-
[4-(methylsulfonyl)phenyl]-1H-pyrrole (Example 1)
10 (1.55 g, 4.71 mmol) in dimethylformamide (3.65 ml, 47
mmol) and toluene (20 ml), phosphorous oxychloride
(3.5 ml, 37.7 mmol) was added. After stirring for 20
minutes, the reaction mixture was heated at 70 °C for
5 hours. The reaction mixture was cooled, poured into
15 aqueous sodium acetate solution and extracted with
ethyl acetate. The organic fractions were washed with
10% aqueous potassium carbonate and water. After
drying (Na₂SO₄), filtration and concentration, the
crude yellowish liquid (2.06 g) was purified by
20 chromatography (silica gel, hexane/ethyl acetate, 6/4)
to give 1-(4-fluorophenyl)-2-methyl-5-[4-
(methylsulfonyl)phenyl]-1H-pyrrole-3-carboxaldehyde
(1.2 g, 71%): mp (DSC) 155 °C. Anal Calc'd. for
C₁₉H₁₆NSFO₃: C, 63.85; H, 4.51; N, 3.92. Found: C,
25 63.50; H, 4.66; N, 3.85.

Example 19

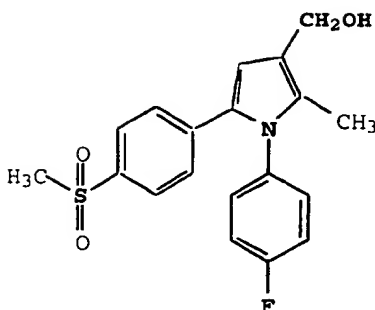
5 **3-Bromo-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole**

To a solution of 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole (Example 1) (3.3
10 g, 10 mmol) in THF (80 ml) at -70 °C, *N*-bromosuccinimide (1.78 g, 10 mmol) was added over 10 minutes. The reaction was warmed to 20 °C over 3 hours and stirred for 18 hours. After dilution with aqueous sodium bicarbonate, the mixture was extracted with
15 ethyl acetate. The organic fractions were washed with water, dried (MgSO₄), filtered and concentrated. The crude yellowish liquid (4.52 g) was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3) to give 3-bromo-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole (3.6 g, 88%): mp
20 (DSC) 153 °C. Anal Calc'd. for C₁₈H₁₅NSBrFO₂: C, 52.95; H, 3.70; N, 3.43; S, 19.53. Found: C, 53.01; H, 3.93; N, 3.39; S, 19.06.

Example 20

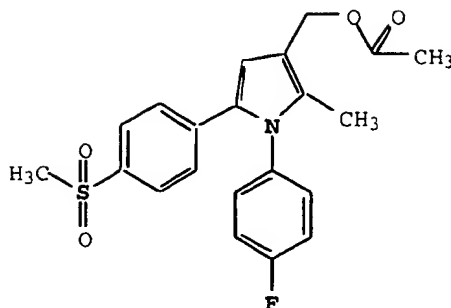
5 **3-Chloro-1-(4-fluorophenyl)-2-methyl-5-[-4-(methylsulfonyl)phenyl]-1H-pyrrole**

To a solution of 1-(4-fluorophenyl)-2-methyl-5-
[4-(methylsulfonyl)phenyl]-1H-pyrrole (Example 1) (1
10 g, 3.03 mmol) in THF (100 ml) at -70 °C, *N*-
chlorosuccinimide (488 mg, 3.65 mmol) was added over
10 minutes. The reaction mixture was warmed to 20 °C
over 3 hours and stirred for 18 hours. More *N*-
chlorosuccinimide (450 mg, 3.37 mmol) was added and
15 the mixture was stirred for 6 hours. After dilution
with aqueous potassium carbonate, the reaction mixture
was extracted with ethyl acetate. The organic
fractions were washed with water, dried (MgSO₄),
filtered and concentrated. The crude dark orange solid
20 (1.3 g) was purified by chromatography (silica gel,
hexane/ethyl acetate, 1/1) to give 3-chloro-1-(4-
fluorophenyl)-2-methyl-5-[-4-(methylsulfonyl)phenyl]-
1H-pyrrole (107 mg, 10%): mp (DSC) 172 °C. Anal
Calc'd. for C₁₈H₁₅NSClFO₂: C, 59.42; H, 4.16; N, 3.85.
25 Found: C, 59.21; H, 4.10; N, 3.56.

Example 21

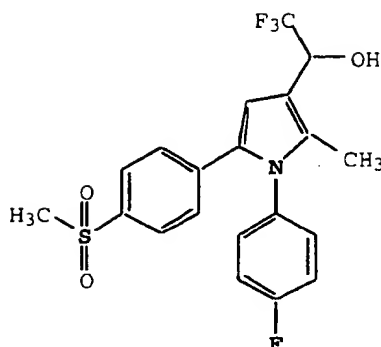
5 **1-(4-Fluorophenyl)-2-methyl-5-[4-**
 (methylsulfonyl)phenyl]-1H-pyrrole-3-methanol

To a solution of 1-(4-fluorophenyl)-2-methyl-5-
[4-(methylsulfonyl)phenyl]-1H-pyrrole-3-carboxaldehyde
10 (Example 18) (1.4 g, 3.9 mmol) in EtOH (30 ml), sodium
borohydride (297 mg, 7.84 mmol) was added. After
heating at reflux for 3 hours, the reaction mixture
was cooled to room temperature and quenched with
acetic acid. The solvent was removed under reduced
15 pressure and the residue was redissolved in methylene
chloride. After washing with 1N HCl and brine, the
organic fractions were filtered, concentrated and
purified by chromatography (silica gel, hexane/ethyl
acetate, 1/1) to give 1-(4-fluorophenyl)-2-methyl-5-
20 [4-(methylsulfonyl)phenyl]-1H-pyrrole-3-methanol (1.4
g, 100%) as a white solid: mp (DSC) 148 °C. Anal
Calc'd. for C₁₉H₁₈NSFO₃·0.4 H₂O: C, 62.25; H, 5.17; N,
3.82; S, 8.75. Found: C, 62.29; H, 4.87; N, 3.86; S,
8.86.

Example 22

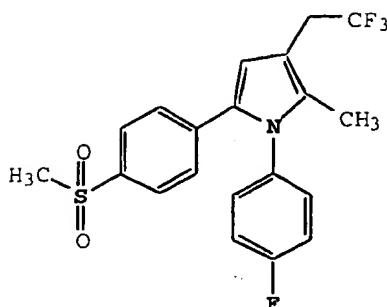
5 **[1-(4-Fluorophenyl)-2-methyl-5-[4-**
 (methylsulfonyl)phenyl]-1H-pyrrol-3-yl]methyl acetate

To a solution of 1-(4-fluorophenyl)-2-methyl-5-
[4-(methylsulfonyl)phenyl]-1H-pyrrole (Example 1) (500
10 mg, 2.87 mmol) in AcOH (5 ml), formaldehyde (0.22 ml,
40% solution in water, 2.87 mmol) was added. After
heating at 50-55 °C for 90 minutes, the reaction
mixture was cooled and poured over ice. The solution
was made alkaline with 2N NaOH and extracted with
15 methylene chloride. The organic fractions were washed
with water and with brine, dried (MgSO₄), filtered and
concentrated to give the crude product (780 mg) as a
yellowish liquid. Chromatography (silica gel,
hexane/ethyl acetate, 6/4) gave [1-(4-fluorophenyl)-2-
20 methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-
yl]methyl acetate (250 mg, 22%) as a white solid: mp
(DSC) 151 °C. Anal Calc'd. for C₂₁H₂₀NSFO₄: C, 62.83;
H, 5.02; N, 3.49. Found: C, 62.48; H, 5.16; N, 3.37.

Example 23

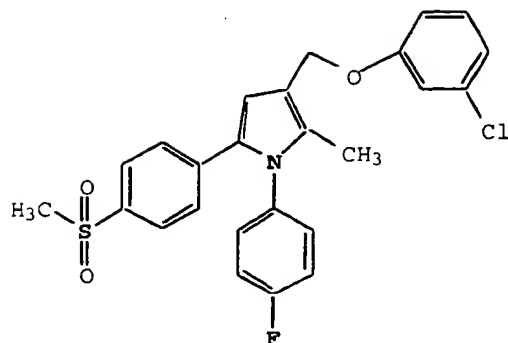
5 **1-(4-Fluorophenyl)-2-methyl-5-[4-**
 (methylsulfonyl)phenyl]-α,α,α-(trifluoromethyl)-1H-
 pyrrole-3-methanol

To a solution of 2,2,2-trifluoro-1-[1-(4-
 10 fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-
 1H-pyrrol-3-yl]ethanone (Example 13) (310 mg, 0.73
 mmol) in ethanol (10 ml) and acetic acid (10 ml), 4%
 Pd/C (51 mg) was added. The system was sealed, purged
 15 with nitrogen (5 times), with hydrogen (5 times) and
 then pressurized to 5 psi hydrogen. After for 24
 hours, the system was vented, purged with nitrogen and
 filtered. The filtrate was concentrated and the crude
 (325 mg) was purified by chromatography (silica gel,
 hexane/ethyl acetate, 6/4) to give 1-(4-fluorophenyl)-
 20 2-methyl-5-[4-(methylsulfonyl)phenyl]-α,α,α-
 (trifluoromethyl)-1H-pyrrole-3-methanol (270 mg, 87%):
 mp (DSC) 213 °C. Anal Calc'd. for C₂₀H₁₇NSF₄O₃: C,
 56.20; H, 4.01; N, 3.28. Found: C, 56.07; H, 4.08; N,
 3.19.

Example 24

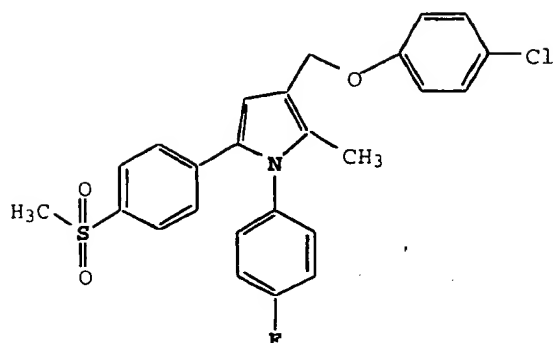
5 **1-(4-Fluorophenyl)-2-methyl-5-[4-**
 (methanesulfonyl)phenyl]-3-(2,2,2-trifluoroethyl)-1H-
 pyrrole

To a solution of 1-(4-fluorophenyl)-2-methyl-5-
10 [4-(methanesulfonyl)phenyl]- α,α,α -(trifluoromethyl)-1H-
pyrrole-3-methanol (Example 23) (325 mg, 0.76 mmol) in
trifluoroacetic acid (5 ml) and acetic acid (10 ml),
5% Pt/C (325 mg) was added. The system was sealed,
purged with nitrogen (5 times), with hydrogen (5
15 times) and then pressurized to 60 psi hydrogen. After
48 hours, the system was vented, purged with nitrogen
and filtered. The filtrate was concentrated, the
residue was redissolved in methylene chloride and
washed with aqueous potassium carbonate and brine.
20 After drying (MgSO₄), filtration and concentration,
the crude (320 mg) was purified by chromatography
(silica gel, hexane/ethyl acetate, 7/3) to give 1-(4-
fluorophenyl)-2-methyl-5-[4-(methanesulfonyl)phenyl]-3-
(2,2,2-trifluoroethyl)-1H-pyrrole (135 mg, 43%): mp
25 (DSC) 151 °C. Anal Calc'd. for C₂₀H₁₇NSF₄O₂·0.25 H₂O:
C, 57.76; H, 4.24; N, 3.37. Found: C, 57.73; H, 4.34;
N, 3.30.

Example 25

5 **3-[(3-Chlorophenoxy)methyl]-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole**

To a solution of 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-3-methanol
10 (Example 21) (300 mg, 0.83 mmol), 3-chlorophenol (88 μ l, 0.83 mmol), and triphenylphosphine (219 mg, 0.83 mmol) in THF (20 ml), diethyl azodicarboxylate (132 μ l, 0.83 mmol) was added. The mixture was stirred at room temperature for 48 hours. The solvent was removed
15 under reduced pressure and the crude liquid (820 mg) was purified by chromatography (silica gel, hexane/ethyl acetate, 7/3) to give 3-[(3-chlorophenoxy)methyl]-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole (75 mg, 19%): mp
20 (DSC) 139 °C. Anal Calc'd. for $C_{25}H_{21}NSClFO_3$: C, 63.89; H, 4.50; N, 2.98. Found: C, 63.85; H, 4.98; N, 2.76.

Example 26

5 **3-[(4-Chlorophenoxy)methyl]-1-(4-fluorophenyl)-2-**
 methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole

To a solution of 1-(4-fluorophenyl)-2-methyl-5-
[4-(methylsulfonyl)phenyl]-1H-pyrrole-3-methanol
10 (Example 21) (300 mg, 0.83 mmol), 4-chlorophenol (107
mg, 0.83 mmol), and triphenylphosphine (219 mg, 0.83
mmol) in THF (20 ml), diethyl azodicarboxylate (132
μl, 0.83 mmol) was added. The mixture was stirred at
room temperature for 48 hours. The solvent was removed
15 under reduced pressure and the crude (830 mg) was
purified by chromatography (silica gel, hexane/ethyl
acetate, 1/1) to give 3-[(4-chlorophenoxy)methyl]-1-
(4-fluorophenyl)-2-methyl-5-[4-
(methylsulfonyl)phenyl]-1H-pyrrole (29 mg, 7%): mp
20 (DSC) 145 °C. Anal Calc'd. for C₂₅H₂₁NSClFO₃·0.25 H₂O:
C, 63.29; H, 4.57; N, 2.95. Found: C, 63.46; H, 4.57;
N, 2.81.

BIOLOGICAL EVALUATION

25 Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed
with materials, reagents and procedures essentially as
described by Winter, et al., (*Proc. Soc. Exp. Biol.*
Med., **111**, 544 (1962)). Male Sprague-Dawley rats were

selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Otterness and Bliven, *Laboratory Models for Testing NSAIDs*, in **Non-steroidal Anti-Inflammatory Drugs**, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table I.

25

TABLE I.

	RAT PAW EDEMA	ANALGESIA
	% Inhibition	% Inhibition
Example	@ 30mg/kg body weight	@ 30mg/kg body weight
8	56	47

30

Evaluation of COX-1 and COX-2 activity *in vitro*

The compounds of this invention exhibited inhibition *in vitro* of COX-2. The COX-2 inhibition activity of the compounds of this invention

35

illustrated in the Examples was determined by the following methods.

a. Preparation of recombinant COX baculoviruses

Recombinant COX-1 and COX-2 were prepared as described by Gierse et al, [*J. Biochem.*, **305**, 479-84 (1995)]. A 2.0 kb fragment containing the coding region of either human or murine COX-1 or human or murine COX-2 was cloned into a BamH1 site of the baculovirus transfer vector pVL1393 (Invitrogen) to generate the baculovirus transfer vectors for COX-1 and COX-2 in a manner similar to the method of D.R. O'Reilly et al (*Baculovirus Expression Vectors: A Laboratory Manual* (1992)). Recombinant baculoviruses were isolated by transfecting 4 µg of baculovirus transfer vector DNA into SF9 insect cells (2×10^8) along with 200 ng of linearized baculovirus plasmid DNA by the calcium phosphate method. See M.D. Summers and G.E. Smith, *A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures*, Texas Agric. Exp. Station Bull. 1555 (1987). Recombinant viruses were purified by three rounds of plaque purification and high titer (10^7 - 10^8 pfu/mL) stocks of virus were prepared. For large scale production, SF9 insect cells were infected in 10 liter fermentors (0.5×10^6 /mL) with the recombinant baculovirus stock such that the multiplicity of infection was 0.1. After 72 hours the cells were centrifuged and the cell pellet homogenized in Tris/Sucrose (50 mM: 25%, pH 8.0) containing 1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). The homogenate was centrifuged at 10,000xG for 30 minutes, and the resultant supernatant was stored at -80°C before being assayed for COX activity.

b. Assay for COX-1 and COX-2 activity

COX activity was assayed as PGE₂ formed/µg protein/time using an ELISA to detect the prostaglandin released. CHAPS-solubilized insect cell

membranes containing the appropriate COX enzyme were incubated in a potassium phosphate buffer (50 mM, pH 8.0) containing epinephrine, phenol, and heme with the addition of arachidonic acid (10 μ M). Compounds were pre-incubated with the enzyme for 10-20 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after ten minutes at 37 °C/room temperature by transferring 40 μ l of reaction mix into 160 μ l ELISA buffer and 25 μ M indomethacin. The PGE₂ formed was measured by standard ELISA technology (Cayman Chemical). Results are shown in Table II.

TABLE II.

Example		COX-2	COX-1
		IC50 μ M	IC50 μ M
15	1	<0.1	>100
	2	0.2	>100
	3	0.3	>100
20	4	<0.1	>100
	5	<0.1	>100
	6	2.9	>100
	7	0.5	62.4
	8	0.5	>100
25	9	0.3	10.4
	10	10.2	>100
	11	<0.1	3.8
	13	0.1	>10
	14	1.6	>100
30	15	1.0	>30
	16	<0.1	>100
	17	0.8	>100
	18	3.2	>100
	19	<0.1	0.8
35	20	<0.1	4.5
	21	3.9	>100
	22	0.5	>100

TABLE II.

Example		COX-2	COX-1
		IC50 μ M	IC50 μ M
5	23	1.4	>100
	24	0.1	>100
	25	<0.1	>100
	26	<0.1	>100

10 Also embraced within this invention is a class of
pharmaceutical compositions comprising the active
compounds of Formula I in association with one or more
non-toxic, pharmaceutically-acceptable carriers and/or
15 diluents and/or adjuvants (collectively referred to
herein as "carrier" materials) and, if desired, other
active ingredients. The active compounds of the
present invention may be administered by any suitable
route, preferably in the form of a pharmaceutical
composition adapted to such a route, and in a dose
20 effective for the treatment intended. The active
compounds and composition may, for example, be
administered orally, intravascularly,
intraperitoneally, subcutaneously, intramuscularly or
topically.

25 The phrase "co-therapy" (or "combination-
therapy"), in defining use of a cyclooxygenase-2
inhibitor agent and another pharmaceutical agent, is
intended to embrace administration of each agent in a
sequential manner in a regimen that will provide
30 beneficial effects of the drug combination, and is
intended as well to embrace co-administration of these
agents in a substantially simultaneous manner, such as
in a single capsule having a fixed ratio of these
active agents or in multiple, separate capsules for
35 each agent.

 The phrase "therapeutically-effective" is
intended to qualify the amount of each agent which

severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

5 For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the
10 active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

15 The amount of therapeutically active compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical
20 condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000
25 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.5 and about 20 mg/kg body weight and most preferably between about 0.1 to 10
30 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

 In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the
35 affected area two to four times a day.

 For inflammations of the eye or other external tissues, e.g., mouth and skin, the formulations are

preferably applied as a topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and

an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a

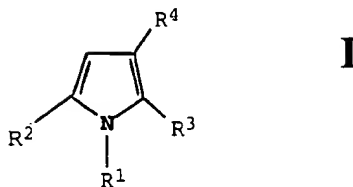
concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

For therapeutic purposes, the active compounds of this combination invention are ordinarily combined
5 with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid,
10 magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient
15 administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic
20 sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved
25 in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.
30 All mentioned references are incorporated by reference as if here written.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

CLAIMS:

1. A compound of Formula I



- 5 wherein R^1 and R^2 are independently selected from aryl, cycloalkyl, cycloalkenyl and heterocyclyl, wherein R^1 and R^2 are optionally substituted at a substitutable position with one or more radicals independently selected from alkylsulfonyl, aminosulfonyl, haloalkylsulfonyl, halo, alkylthio, alkylsulfinyl, alkyl, cyano, carboxyl, alkoxycarbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, haloalkoxy, amino, alkylamino, arylamino and nitro;
- 10 wherein R^3 is a radical selected from hydrido, halo, methyl and alkoxycarbonylalkyl; and wherein R^4 is a radical selected from hydrido, halo, alkyl, haloalkyl, cyano, alkoxycarbonyl, carboxyl, formyl, aryl, heteroaryl, alkylsulfonyl, haloalkylsulfonyl, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, carboxyalkyl, alkoxycarbonylalkyl, alkylcarbonyloxyalkyl, mercaptoalkyl, alkylthioalkyl, haloalkylcarbonyl, haloalkyl(hydroxy)alkyl, aminoalkyl, alkylaminoalkyl and alkoxy;
- 20 provided one of R^1 and R^2 is phenyl substituted with methylsulfonyl or aminosulfonyl and the other is selected from optionally substituted cycloalkyl, optionally substituted cycloalkenyl and optionally substituted heterocyclyl; and further provided R^3 is hydrido when R^1 is phenyl substituted with aminosulfonyl or methylsulfonyl;
- 30 or a pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein R^1 and R^2 are independently selected from phenyl, lower cycloalkyl, lower cycloalkenyl and 5- or 6-membered heteroaryl,
- 35

wherein R¹ and R² are optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfonyl, aminosulfonyl, lower haloalkylsulfonyl, halo, lower alkylthio, lower alkyl, cyano, carboxyl, lower alkoxy carbonyl, lower alkyl carbonyl, lower haloalkyl, hydroxyl, lower alkoxy, lower hydroxyalkyl, lower alkoxyalkyl, lower haloalkoxy, amino, lower alkylamino, arylamino and nitro; wherein R³ is a radical selected from hydrido, halo, methyl and lower alkoxy carbonylalkyl; and wherein R⁴ is a radical selected from hydrido, halo, lower alkyl, lower haloalkyl, cyano, lower alkoxy carbonyl, carboxyl, formyl, phenyl, 5- or 6-membered heteroaryl, lower alkylsulfonyl, lower haloalkylsulfonyl, lower hydroxyalkyl, lower alkoxyalkyl, lower alkyl carbonyl, lower carboxyalkyl, lower alkoxy carbonylalkyl, lower alkyl carbonyloxyalkyl, lower mercaptoalkyl, lower alkylthioalkyl, lower haloalkyl carbonyl, lower haloalkyl(hydroxy)alkyl, lower aminoalkyl, lower alkylaminoalkyl and lower alkoxy; or a pharmaceutically-acceptable salt thereof.

3. Compound of Claim 2 wherein R¹ and R² are independently selected from phenyl, cyclohexyl, cyclohexenyl, benzofuryl, benzodioxolyl, furyl, imidazolyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, isoxazolyl, triazolyl, pyrimidinyl, isoquinolyl, quinolinyl, benzimidazolyl, indolyl, pyrazolyl and pyridyl, wherein R¹ and R² are optionally substituted at a substitutable position with one or more radicals independently selected from methylsulfonyl, aminosulfonyl, fluoromethylsulfonyl, difluoromethylsulfonyl, fluoro, chloro, bromo, methylthio, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl,

- isobutoxycarbonyl, pentoxycarbonyl, methylcarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl,
- 5 difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl,
- 10 trifluoromethoxy, amino, methylamino, N,N-dimethylamino, phenylamino and nitro; wherein R³ is a radical selected from hydrido, fluoro, chloro, bromo, methyl, ethoxycarbonylethyl, and methoxycarbonylmethyl; and wherein R⁴ is a radical
- 15 selected from hydrido, fluoro, chloro, bromo, methyl, ethyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyano, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, carboxyl, formyl, phenyl, methylsulfonyl, trifluoromethylsulfonyl,
- 20 hydroxymethyl, hydroxyethyl, methoxymethyl, ethoxymethyl, methylcarbonyl, ethylcarbonyl, trifluoromethylcarbonyl, trifluoro(hydroxy)ethyl, methoxycarbonylmethyl, ethoxycarbonylethyl, carboxymethyl, carboxypropyl,
- 25 methylcarbonyloxymethyl, thienyl, furyl, and pyridyl, wherein the thienyl, furyl, pyridyl and phenyl radicals are optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio,
- 30 methylsulfinyl, methyl, ethyl, isopropyl, tert-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl,
- 35 dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy,

hydroxymethyl, hydroxyethyl and trifluoromethoxy; or
a pharmaceutically-acceptable salt thereof.

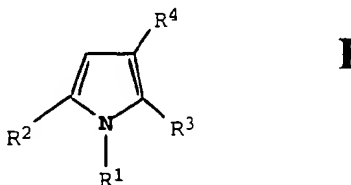
4. Compound of Claim 1 selected from compounds,
5 and their pharmaceutically acceptable salts, of the
group consisting of
1-cyclohexyl-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-
pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(4-pyridyl)-1H-
10 pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(3-pyridyl)-1H-
pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(2-pyridyl)-1H-
pyrrole;
15 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(4-methyl-2-
pyridyl)-1H-pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(4-methyl-3-
pyridyl)-1H-pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(5-methyl-2-
20 pyridyl)-1H-pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(5-methyl-3-
pyridyl)-1H-pyrrole;
2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(3-methyl-2-
pyridyl)-1H-pyrrole;
25 2-methyl-5-[4-(methylsulfonyl)phenyl]-1-(2-methyl-3-
pyridyl)-1H-pyrrole;
4-[1-(cyclohexyl)-2-methyl-1H-pyrrol-5-
yl]benzenesulfonamide;
4-[2-methyl-1-(4-pyridyl)-1H-pyrrol-5-
30 yl]benzenesulfonamide;
5-[4-(methylsulfonyl)phenyl]-1-(4-pyridyl)-1H-pyrrole;
5-[4-(methylsulfonyl)phenyl]-1-(3-pyridyl)-1H-pyrrole;
5-[4-(methylsulfonyl)phenyl]-1-(2-pyridyl)-1H-pyrrole;
5-[4-(methylsulfonyl)phenyl]-1-(4-methyl-2-pyridyl)-1H-
35 pyrrole;
5-[4-(methylsulfonyl)phenyl]-1-(4-methyl-3-pyridyl)-1H-
pyrrole;

- 5-[4-(methylsulfonyl)phenyl]-1-(5-methyl-2-pyridyl)-1H-pyrrole;
- 5-[4-(methylsulfonyl)phenyl]-1-(5-methyl-3-pyridyl)-1H-pyrrole;
- 5 5-[4-(methylsulfonyl)phenyl]-1-(3-methyl-2-pyridyl)-1H-pyrrole;
- 5-[4-(methylsulfonyl)phenyl]-1-(2-methyl-3-pyridyl)-1H-pyrrole;
- 4-[1-(cyclohexyl)-1H-pyrrol-5-yl]benzenesulfonamide;
- 10 4-[1-(4-pyridyl)-1H-pyrrol-5-yl]benzenesulfonamide;
- 1-[4-(methylsulfonyl)phenyl]-5-(4-pyridyl)-1H-pyrrole;
- 1-[4-(methylsulfonyl)phenyl]-5-(3-pyridyl)-1H-pyrrole;
- 1-[4-(methylsulfonyl)phenyl]-5-(2-pyridyl)-1H-pyrrole;
- 1-[4-(methylsulfonyl)phenyl]-5-(4-methyl-2-pyridyl)-1H-
- 15 pyrrole;
- 1-[4-(methylsulfonyl)phenyl]-5-(4-methyl-3-pyridyl)-1H-pyrrole;
- 1-[4-(methylsulfonyl)phenyl]-5-(5-methyl-2-pyridyl)-1H-pyrrole;
- 20 1-[4-(methylsulfonyl)phenyl]-5-(5-methyl-3-pyridyl)-1H-pyrrole;
- 1-[4-(methylsulfonyl)phenyl]-5-(3-methyl-2-pyridyl)-1H-pyrrole;
- 1-[4-(methylsulfonyl)phenyl]-5-(2-methyl-3-pyridyl)-1H-
- 25 pyrrole;
- 4-[5-(cyclohexyl)-1H-pyrrol-1-yl]benzenesulfonamide;
- 4-[5-(4-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
- 4-[5-(3-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
- 4-[5-(2-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
- 30 4-[5-(4-methyl-3-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
- 4-[5-(4-methyl-2-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;
- 4-[5-(5-methyl-3-pyridyl)-1H-pyrrol-1-
- 35 yl]benzenesulfonamide;
- 4-[5-(5-methyl-2-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide;

4-[5-(2-methyl-3-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide; and
 4-[5-(3-methyl-2-pyridyl)-1H-pyrrol-1-yl]benzenesulfonamide.

5

5. A compound of Formula I



10 wherein R^1 and R^2 are independently selected from aryl optionally substituted at a substitutable position with one or more radicals independently selected from alkylsulfonyl, aminosulfonyl, haloalkylsulfonyl, halo, alkylthio, alkylsulfinyl, alkyl, cyano, carboxyl, alkoxy carbonyl, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, alkoxyalkyl, alkylcarbonyl, haloalkoxy, amino, alkylamino, arylamino and nitro;

15 wherein R^3 is a radical selected from hydrido, halo, methyl and alkoxy carbonylalkyl; and

20 wherein R^4 is a radical selected from halo, cyano, alkoxy carbonyl, carboxyl, formyl, aryl, heteroaryl, alkylsulfonyl, haloalkylsulfonyl, alkylcarbonyl, carboxyalkyl, alkoxy carbonylalkyl, alkylcarbonyloxyalkyl, haloalkylcarbonyl, aminoalkyl, 25 alkylaminoalkyl and alkoxy;

provided at least one of R^1 and R^2 is phenyl substituted with methylsulfonyl or aminosulfonyl;

or a pharmaceutically-acceptable salt thereof.

30 6. Compound of Claim 5 wherein R^1 and R^2 are phenyl, optionally substituted at a substitutable position with one or more radicals independently selected from lower alkylsulfonyl, aminosulfonyl, lower haloalkylsulfonyl, halo, lower alkylthio, lower alkyl, cyano, carboxyl, lower alkoxy carbonyl, lower

35

alkylcarbonyl, lower haloalkyl, hydroxyl, lower
alkoxy, lower hydroxyalkyl, lower alkoxyalkyl, lower
haloalkoxy, amino, lower alkylamino, arylamino and
nitro; wherein R³ is a radical selected from hydrido,
5 halo, methyl and lower alkoxyalkyl; and
wherein R⁴ is a radical selected from halo, cyano,
lower alkoxyalkyl, carboxyl, formyl, phenyl, 5- or
6-membered heteroaryl, lower alkylsulfonyl, lower
haloalkylsulfonyl, lower alkylcarbonyl, lower
10 carboxyalkyl, lower alkoxyalkyl, lower
alkylcarbonyloxyalkyl, lower haloalkylcarbonyl, lower
aminoalkyl, lower alkylaminoalkyl and lower alkoxy;
or a pharmaceutically-acceptable salt thereof.

7. Compound of Claim 6 wherein R¹ and R² are
15 independently selected from phenyl optionally
substituted at a substitutable position with one or
more radicals independently selected from
methylsulfonyl, aminosulfonyl, fluoromethylsulfonyl,
difluoromethylsulfonyl, fluoro, chloro, bromo,
20 methylthio, methyl, ethyl, isopropyl, tert-butyl,
isobutyl, pentyl, hexyl, cyano, carboxyl,
methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl,
tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl,
isobutoxycarbonyl, pentoxycarbonyl, methylcarbonyl,
25 fluoromethyl, difluoromethyl, trifluoromethyl,
chloromethyl, dichloromethyl, trichloromethyl,
pentafluoroethyl, heptafluoropropyl,
difluorochloromethyl, dichlorofluoromethyl,
difluoroethyl, difluoropropyl, dichloroethyl,
30 dichloropropyl, hydroxyl, methoxy, methylenedioxy,
ethoxy, propoxy, n-butoxy, hydroxymethyl,
hydroxyethyl, methoxymethyl, ethoxymethyl,
trifluoromethoxy, amino, methylamino, N,N-
dimethylamino, phenylamino and nitro; wherein R³ is a
35 radical selected from hydrido, fluoro, chloro, bromo,
methyl, ethoxycarbonyl, and
methoxycarbonylmethyl; and wherein R⁴ is a radical

selected from fluoro, chloro, bromo, cyano, methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, carboxyl, formyl, phenyl, methylsulfonyl, trifluoromethylsulfonyl, methylcarbonyl, ethylcarbonyl, trifluoromethylcarbonyl, methoxycarbonylmethyl, ethoxycarbonylethyl, carboxymethyl, carboxypropyl, methylcarbonyloxymethyl, thienyl, furyl, and pyridyl, wherein the thienyl, furyl, pyridyl and phenyl radicals are optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methylsulfinyl, methyl, ethyl, isopropyl, *tert*-butyl, isobutyl, pentyl, hexyl, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, *n*-butoxy, hydroxymethyl, hydroxyethyl and trifluoromethoxy; or a pharmaceutically-acceptable salt thereof.

8. Compound of Claim 5 selected from compounds, and their pharmaceutically acceptable salts, of the group consisting of

ethyl 1-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-2-propanoate;

2,2,2-trifluoro-1-[1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]ethanone;

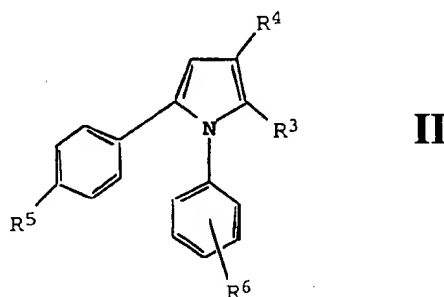
1-[1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]ethanone;

1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-3-[(trifluoromethyl)sulfonyl]-1H-pyrrole;

1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-3-carbonitrile;

1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole-3-carboxaldehyde;
 3-bromo-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole;
 5 3-chloro-1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrole; and
 [1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1H-pyrrol-3-yl]methyl
 acetate.

10 9. A compound of Formula II



wherein R³ is a radical selected from hydrido,
 15 methyl and lower alkoxyacetylalkyl; wherein R⁴ is a
 radical selected from hydrido, halo, cyano, formyl,
 lower haloalkylsulfonyl, lower haloalkyl, lower
 hydroxyalkyl, lower alkylcarbonyl, lower
 haloalkylcarbonyl, lower alkylcarbonyloxyalkyl and
 20 lower haloalkylhydroxyalkyl; wherein R⁵ is
 methylsulfonyl or aminosulfonyl; and wherein R⁶ is one
 or more radicals independently selected from hydrido,
 halo, lower alkyl, lower alkylcarbonyl, and lower
 haloalkyl; provided R⁶ is not fluoro mono-substitution
 25 at phenyl position 4 when R³ is methyl, and when R⁴ is
 hydrido, trifluoromethyl, difluoromethyl or
 hydroxymethyl; or a pharmaceutically-acceptable salt
 thereof.

10. A pharmaceutical composition comprising a
 30 therapeutically-effective amount of a compound, said
 compound selected from a family of compounds of Claim
 1; or a pharmaceutically-acceptable salt thereof.

11. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 2; or a pharmaceutically-acceptable salt thereof.

5 12. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 3; or a pharmaceutically-acceptable salt thereof.

10 13. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 4; or a pharmaceutically-acceptable salt thereof.

15 14. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 5; or a pharmaceutically-acceptable salt thereof.

20 15. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 6; or a pharmaceutically-acceptable salt thereof.

25 16. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 7; or a pharmaceutically-acceptable salt thereof.

17. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 8; or a pharmaceutically-acceptable salt thereof.

30 18. A pharmaceutical composition comprising a therapeutically-effective amount of a compound, said compound selected from a family of compounds of Claim 9; or a pharmaceutically-acceptable salt thereof.

35 19. A method of treating a cyclooxygenase-2 mediated disorder in a subject, said method comprising treating the subject having or susceptible to said disorder with a therapeutically-effective

amount of a compound of Claim 1; or a pharmaceutically-acceptable salt thereof.

20. A method of treating a cyclooxygenase-2 mediated disorder in a subject, said method
5 comprising treating the subject having or susceptible to said disorder with a therapeutically-effective amount of a compound of Claim 2; or a pharmaceutically-acceptable salt thereof.

10 21. A method of treating a cyclooxygenase-2 mediated disorder in a subject, said method comprising treating the subject having or susceptible to said disorder with a therapeutically-effective amount of a compound of Claim 3; or a
15 pharmaceutically-acceptable salt thereof.

22. A method of treating a cyclooxygenase-2 mediated disorder in a subject, said method comprising treating the subject having or susceptible to said disorder with a therapeutically-effective
20 amount of a compound of Claim 4; or a pharmaceutically-acceptable salt thereof.

23. A method of treating a cyclooxygenase-2 mediated disorder in a subject, said method comprising treating the subject having or susceptible
25 to said disorder with a therapeutically-effective amount of a compound of Claim 5; or a pharmaceutically-acceptable salt thereof.

24. A method of treating a cyclooxygenase-2 mediated disorder in a subject, said method
30 comprising treating the subject having or susceptible to said disorder with a therapeutically-effective amount of a compound of Claim 6; or a pharmaceutically-acceptable salt thereof.

25. A method of treating a cyclooxygenase-2
35 mediated disorder in a subject, said method comprising treating the subject having or susceptible to said disorder with a therapeutically-effective

amount of a compound of Claim 7; or a
pharmaceutically-acceptable salt thereof.

26. A method of treating a cyclooxygenase-2
mediated disorder in a subject, said method
5 comprising treating the subject having or susceptible
to said disorder with a therapeutically-effective
amount of a compound of Claim 8; or a
pharmaceutically-acceptable salt thereof.

27. A method of treating a cyclooxygenase-2
10 mediated disorder in a subject, said method
comprising treating the subject having or susceptible
to said disorder with a therapeutically-effective
amount of a compound of Claim 9; or a
pharmaceutically-acceptable salt thereof.

15 28. The method of Claim 19 wherein the
cyclooxygenase-2 mediated disorder is inflammation.

29. The method of Claim 19 wherein the
cyclooxygenase-2 mediated disorder is arthritis.

30. The method of Claim 19 wherein the
20 cyclooxygenase-2 mediated disorder is pain.

31. The method of Claim 19 wherein the
cyclooxygenase-2 mediated disorder is fever.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/22488

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D207/333 A61K31/40 C07D401/04 C07D207/33 C07D207/337
C07D207/36 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0 799 823 A (SANKYO COMPANY LIMITED) 8 October 1997 see the whole document ---	5-18
P,X	KHANNA ET AL. : "1,2-Diarylpyrroles as potent and selective inhibitors of cyclooxygenase-2" JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 11, 1997, pages 1619-33, XP002059990 see the whole document ---	5-18
Y	DE 19 38 904 A (INNOTHERA) 5 February 1970 see page 45-49; claim 1; examples 65,66 --- -/--	1-18

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

24 March 1998

Date of mailing of the international search report

03. 04. 98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lauro, P

International Application No
PCT/US 97/22488

PCT/US 97/22488

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WILKERSON W W ET AL: "ANTIINFLAMMATORY 4,5-DIARYLPYRROLES. 2. ACTIVITY AS A FUNCTION OF CYCLOOXYGENASE-2 INHIBITION" JOURNAL OF MEDICINAL CHEMISTRY, vol. 38, no. 20, 29 September 1995, pages 3895-3901, XP002030129 cited in the application see the whole document ---</p>	1-18
Y	<p>US 3 427 305 A (CHINN ET AL.) 11 February 1969 cited in the application see the whole document ---</p>	1-18
A	<p>THIAULT ET AL.: "N-Arylpyrrole derivatives with analgesic and antiinflammatory activities. Part I. 4,5-Disubstituted 1-arylpyrroles" FARMACO, ED. SCI., vol. 39, no. 6, 1984, pages 524-37, XP002059991 cited in the application see the whole document -----</p>	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/22488

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 799823 A	08-10-97	AU 1665397 A	09-10-97
		CA 2201812 A	05-10-97
		CZ 9701035 A	15-10-97
		JP 9323971 A	16-12-97
		NO 971564 A	06-10-97
DE 1938904 A	05-02-70	FR 2054474 A	23-04-71
		FR 7649 M	02-02-70
		GB 1263940 A	16-02-72
US 3427305 A	11-02-69	NONE	